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(54) Title: CELL SURFACE RECEPTOR ISOFORMS AND METHODS OF IDENTIFYING AND USING THE SAME

(57) Abstract: Isoforms of cell surface receptors, including isoforms of receptor tyrosine kinases and pharmaceutical compositions containing receptor tyrosine kinase isoforms are provided. Chimeras of and conjugates containing the cell surface receptors that contain a portion, such as or a part thereof of an extracellular domain, from one cell surface receptor and a second portion, particularly an intron-encoded portion, from a second cell surface protein also are provided. The isoforms modulate the activity of a cell surface receptor. Methods for identifying and preparing isoforms of cell surface receptors including receptor tyrosine kinases are provided. Also provided are methods of treatment with the cell surface receptor isoforms.

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**CELL SURFACE RECEPTOR ISOFORMS AND  
METHODS OF IDENTIFYING AND USING THE SAME  
RELATED APPLICATIONS**

Benefit of priority is claimed to U.S. Provisional Application Serial No. 60/666,825 to Pei Jin and H. Michael Shepard, filed March 30, 2005, entitled "CELL SURFACE RECEPTOR ISOFORMS AND METHODS OF IDENTIFYING AND USING SAME;" to U.S. Provisional Application Serial No. 60/571,289 to Pei Jin, filed May 14, 2004, entitled "CELL SURFACE RECEPTOR ISOFORMS AND METHODS OF IDENTIFYING AND USING SAME,"; and to U.S. Provisional Application Serial No. 60/580,990 to Pei Jin, filed June 18, 2004, entitled "CELL SURFACE RECEPTOR ISOFORMS AND METHODS OF IDENTIFYING AND USING SAME."

This application also is related to U.S. application Serial No. 10/846,113, filed May 14, 2004, and to corresponding published International PCT application No. WO 05/016966, published February 24, 2005, entitled "INTRON FUSION PROTEINS, AND METHODS OF IDENTIFYING AND USING SAME." This application also is related to U.S. Application Serial No. 11/129,746 to Pei Jin and H. Michael Shepard, entitled "CELL SURFACE RECEPTOR ISOFORMS AND METHODS OF IDENTIFYING AND USING THE SAME," filed the same day herewith.

Where permitted, the subject matter of each of these applications, provisional applications and international applications is incorporated herein by reference thereto.

**FIELD OF THE INVENTION**

Isoforms of cell surface receptors, including isoforms of receptor tyrosine kinases and pharmaceutical compositions containing receptor tyrosine kinase isoforms are provided. The cell surface receptor isoforms and compositions containing them can be used in methods of treatment of diseases, such as cancer and inflammatory disease.

**BACKGROUND**

Cell signaling pathways involve a network of molecules including polypeptides and small molecules that interact to relay extracellular, intercellular and intracellular signals. Such pathways interact like a relay, handing off signals from



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one member of the pathway to the next. Modulation of one member of the pathway can be relayed through the signal transduction pathway, resulting in modulation of activities of other pathway members and modulating outcomes of such signal transduction such as affecting phenotypes and responses of a cell or organism to a  
5 signal. Diseases and disorders can involve misregulated or changes in modulation of signal transduction pathways. A goal of drug development is to target such misregulated pathways to restore more normal regulation in the signal transduction pathway.

Receptor tyrosine kinases (RTKs) are among the polypeptides involved in  
10 many signal transduction pathways. RTKs play a role in a variety of cellular processes, including cell division, proliferation, differentiation, migration and metabolism. RTKs can be activated by ligands. Such activation in turn activates events in a signal transduction pathway, such as by triggering autocrine or paracrine cellular signaling pathways, for example, activation of second messengers, which  
15 results in specific biological effects. Ligands for RTKs specifically bind to the cognate receptors.

RTKs have been implicated in a number of diseases including cancers such as breast and colorectal cancers, gastric carcinoma, gliomas and mesodermal-derived tumors. Disregulation of RTKs has been noted in several cancers. For example,  
20 breast cancer can be associated with amplified expression of p185-HER2. RTKs also have been associated with diseases of the eye, including diabetic retinopathies and macular degeneration. RTKs also are associated with regulating pathways involved in angiogenesis, including physiologic and tumor blood vessel formation. RTKs also are implicated in the regulation of cell proliferation, migration and survival.

25 The human epidermal growth factor receptor 2 gene (HER-2; also referred to as ErbB2) encodes a receptor tyrosine kinase that has been implicated as an oncogene. HER-2 has a major mRNA transcript of 4.5 Kb that encodes a polypeptide of about 185 kD (P185HER2). P185HER2 contains an extracellular domain, a transmembrane domain and an intracellular domain with tyrosine kinase activity. Several polypeptide  
30 forms are produced from the HER-2 gene and include polypeptides generated by proteolytic processing and forms generated from

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alternatively spliced RNAs. Herstatins and fragments thereof are HER-2 binding proteins, encoded by the HER-2 gene. Herstatins (also referred to as p68HER-2) are encoded by an alternatively spliced variant of the gene encoding the p185-HER2 receptor. For example, one Herstatin occurs in fetal kidney and liver, and includes a  
5 79 amino acid intron-encoded insert, relative to the membrane-localized receptor, at the C terminus (see U.S. Patent No. 6,414,130 and U.S. Published Application No. 20040022785). Several Herstatin variants have been identified (see, *e.g.*, U.S. Patent No. 6,414,130; U.S. Published Application No. 20040022785, U.S. appln. Serial No. 09/234,208; U.S. appln. Serial No. 09/506,079; published international application  
10 Nos. WO0044403 and WO0161356). Herstatins lack an epidermal growth factor (EGF) homology domain and contain part of the extracellular domain, typically the first 340 amino acids, of p185-HER2. Herstatins contain subdomains I and II of the human epidermal growth factor receptor, the HER-2 extracellular domain and a C-terminal domain encoded by an intron. The resulting herstatin polypeptides typically  
15 contain 419 amino acids (340 amino acids from subdomains I and II, plus 79 amino acids from intron 8). The herstatin proteins lack extracellular domain IV, as well as the transmembrane domain and kinase domain.

In contrast, positive acting EGFR ligands, such as the epidermal growth factor and transforming growth factor-alpha, possess such domains. Additionally, binding  
20 of a herstatin does not activate the receptor. Herstatins can inhibit members of the EGF-family of receptor tyrosine kinases as well as the insulin-like growth factor-1 (IGF-1) receptor and other receptors. Herstatins prevent the formation of productive receptor dimers (homodimers and heterodimers) required for transphosphorylation and receptor activation. Alternatively or additionally, herstatin can compete with a  
25 ligand for binding to the receptor terminus (see, U.S. Patent No. 6,414,130; U.S. Published Application No. 20040022785, U.S. appln. Serial No. 09/234,208; U.S. appln. Serial No. 09/506,079; published international application Nos. WO0044403 and WO0161356).

The tumor necrosis factor family of receptors (TNFRs) is another example of a  
30 family of receptors involved in signal transduction and regulation. The TNF ligand and receptor family regulate a variety of signal transduction pathways including those

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involved in cell differentiation, activation, and viability. TNFRs contain an extra-cellular domain, including a ligand binding domain, a transmembrane domain and an intracellular domain that participates in signal transduction. Additionally, TNFRs are typically trimeric proteins that trimerize at the cell surface. TNFRs play a role in  
5 inflammatory diseases, central nervous system diseases, autoimmune diseases, airway hyper-responsiveness conditions such as in asthma, rheumatoid arthritis and inflammatory bowel disease. TNFRs also play a role in infectious diseases, such as viral infection.

The TNF family of receptors (TNFR) exhibit homology among the extra-cellular domains. Some of these receptors initiate apoptosis, some initiate cell proliferation and some initiate both activities. Signaling by this family requires clustering of the receptors by trimeric ligand and subsequent association of proteins with the cytoplasmic region of the receptors. The TNFR family contains a sub family with homologous cytoplasmic 80-amino-acid domains. This domain is referred to as a  
15 death domain (DD), so named because proteins that contain this domain are involved in apoptosis. The distinction between members of the TNFR family is exemplified by two TNFRs coded by distinct genes. TNFRI (55 kDa) signals the initiation of apoptosis and the activation of the transcription factor NFkB. TNFRII (75 kDa) functions to signal activation of NFkB but not the initiation of apoptosis. TNFRI  
20 contains a DD; TNFRII does not.

Because of their involvement in a variety of diseases and conditions, cell surface receptors (CSRs) such as RTKs and TNFRs are targets for therapeutic intervention. Small molecule therapeutics that target RTKs have been designed. While it may be possible to design small molecules as therapeutics that target cell  
25 surface receptors and/or other receptors, there, however, are a number of limitations with such strategies. Small molecules can be limited to interactions with one receptor and thus unable to address conditions where multiple family members may be misregulated. Small molecules also can be promiscuous and affect receptors other than the intended target. Additionally, some small molecules bind irreversibly or  
30 substantially irreversibly to the receptors (*i.e.* subnanomolar binding affinity). The merits of such approaches have not been validated. Antibodies against receptor

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and/or receptor ligands can be used as therapeutics. Antibody treatments, however, can result in an immune response in a subject and thus, such treatments often need extensive tailoring to avoid complications in treatment. Thus, there exists an unmet need for therapeutics for treatment of diseases, including cancers and other diseases

5 involving undesirable cell proliferation and inflammatory reactions, involving cell surface receptors that exhibit RTK activity and/or other cell surface proteins. Accordingly, among the objects herein, it is an object to provide such therapeutics and methods for identifying or discovering candidate therapeutics and methods of treatment.

## 10 SUMMARY

Therapeutic molecules for treating diseases and disorders involving the signal transduction pathways and other cell surface receptor interactions are provided. The therapeutic molecules particularly target RTKs that participated in signal transduction pathways, including those involved in angiogenesis and neovascularization and cell

15 proliferation, particular aberrant angiogenesis, neovascularization and/or cell proliferation. Also provided are compositions containing the molecules and methods for treating diseases and conditions, particularly diseases that include or exhibit or are manifested by aberrant angiogenesis, neovascularization and/or cell proliferation.

Also provided are methods for identifying candidate therapeutics and methods of

20 treatment by administering therapeutic molecules and compositions. The therapeutic molecules can be used for treating any such disease or disorder and exhibit activity, whereby such treatment is effective. Diseases and disorders including proliferative disorders, include tumors, immune disorders and inflammatory disorders. Targets include cells involved in angiogenesis and neovascularization and cells involved in

25 inflammatory responses, cancers and other such disorders. Activity includes modulation of the activity of a cell surface receptor, including RTKs and TNFRs, such as by directly altering the activity by virtue of interaction with the receptor or indirectly by interacting with ligands.

Among the therapeutic molecules provided herein are those that modulate the

30 activity of cellular receptors of angiogenic factors (positive and negative), which serve as points of intervention in a plurality of disease processes. Examples of

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situations in which 'too much' angiogenesis is bad include angiogenesis that supplies blood to tumor foci, or to other sites of disease (such as to the human eye in diabetes). In these cases, therapeutic molecules provided herein that inhibit the process are employed.

5           Activities of the receptor tyrosine kinase (RTK) or TNFR (or other cell surface receptors) modulated by the therapeutic molecules provided herein include, but are not limited to, for example, one or more of dimerization, homodimerization, hetero-dimerization, trimerization, kinase activity, autophosphorylation of the receptor tyrosine kinase, transphosphorylation of the receptor tyrosine kinase, phosphorylation  
10 of a signal transduction molecule, ligand binding, competition with the receptor tyrosine kinase for ligand binding, signal transduction, interaction with a signal transduction molecule, induction of apoptosis, receptor-associated kinase activity, receptor-associated protease activity, membrane association and membrane localization. Modulation includes, for example, inhibition (such as activity as an  
15 antagonist) of an activity and also enhancement (such as activity as an agonist) of an activity. By virtue of modulation of such activity the effects of such receptors are modulated or otherwise modified.

          The therapeutic molecules provided herein typically are polypeptides or peptidomimetics (including polypeptides with modified bonds) or other modified  
20 forms of polypeptides designed, for example, for improved bioavailability, delivery, stability, resistance to proteases and other properties. Contemplated are modifications of the molecules with changes that alter properties, such as bioavailability, protein stability and other such properties, for their use as therapeutics.

          Exemplary of the molecules are polypeptides. Also included are allelic  
25 variants of any of the polypeptides. The allelic variants include any of the variants of the receptor, particularly variants in an extracellular domain, present in a population of the mammal in which a particular receptor occurs. Chimeric molecules, conjugates and conjugates of intron portions of the intron fusion proteins also are provided. The chimeric molecules and conjugates can include portions from molecules with different  
30 ligand binding and/or receptor interacting specificities. For example, conjugates or chimeras that contain an extracellular domain or portion thereof linked directly or

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indirectly to an intron region, such as an intron of a herstatin, are provided. The chimeras and conjugates include portions from CSR isoforms provided herein and known to those of skill in the art including any described in U.S. Provisional Application Serial No. 60/571,289, U.S. Provisional Application Serial No.

5 60/580,990, U.S. application Serial No. 10/846,113, published International PCT application No. WO 05/016966, U.S. Patent No. 6,414,130; U.S. Published Application No. 20040022785, U.S. appln. Serial No. 09/234,208; U.S. appln. Serial No. 09/506,079; published international application Nos. WO0044403 and WO0161356.

10 Isolated polypeptides and variants thereof are provided. The polypeptides are isoforms of cell surface receptors (CSR isoforms) and chimeras and conjugates thereof. Some CSR isoforms, such as intron fusion proteins, are missing all or part of a functional domain or other structural feature such that the activity of the domain is reduced or eliminated and/or a structure is altered compared to the full-length

15 cognate receptor. Other examples include intron fusion proteins in which the rearrangements that occur during alternative splicing can result in either positive or negatively acting molecules. In particular, among the polypeptides provided herein are soluble or non-membrane bound forms of receptors. The polypeptides include a sequence of amino acids that has at least 80%, 85%, 90% or 95% sequence identity

20 with a sequence of amino acids set forth in any of SEQ ID NOS: 91, 93, 95, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, and 226 and allelic variations thereof. Such homology is exhibited along at least 70%, 80%, 85%,

25 90%, 95%, 97% or 100% of the full-length of the polypeptide. Sequence identity is compared along the full length of the polypeptide represented by each SEQ ID to the full length sequence of the isolated polypeptide, and each of SEQ ID NOS: 91, 93, 95, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192,

30 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, and 226 is a cell surface receptor isoform. Exemplary of such polypeptides are isolated

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polypeptides containing the sequence of amino acids set forth in any of SEQ ID NOS: 91, 93, 95, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153 and 155 are provided as are isolated polypeptides that have the sequence of amino acids set forth in any of SEQ ID NOS: 91, 93, 95, 115, 117,  
 5 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153 155, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, and 226. Also provided are chimeras of these molecules and also chimeras of these molecules and herstatins.

10 Provided are isolated polypeptides that are receptor isoforms and that contain at least one domain of a cell surface receptor linked to at least one amino acid encoded by an intron of a gene encoding a cognate cell surface receptor. The cell surface receptor is selected from among DDR1 (discoidin domain receptor), KIT (receptor for c-kit), FGFR-1, FGFR-2, FGFR-4, (fibroblast growth factor receptors 1,  
 15 2 and 4) TNFR2 (tumor necrosis factor receptor), VEGFR-1, VEGFR-2, VEGFR-3, (vascular endothelial growth factor receptors 1,2, and 3), RON (recepteur d'origine nantais; also known as macrophage stimulating 1 receptor), MET (also known as hepatocyte growth factor receptor), TEK (endothelial-specific receptor tyrosine kinase), Tie-1 (tyrosine kinase with immunoglobulin and epidermal growth factor  
 20 homology domains receptor), CSF1R (colony stimulating factor 1 receptor), PDGFR-B (platelet-derived growth factor receptor B), EphA1, EphA2, and EphB1 (erythropoietin-producing hepatocellular receptor A1, A2 and B1, respectively). Exemplary of such polypeptides are those that contain the sequence of amino acids selected from among the sequences of amino acids set forth in SEQ ID NOS: 91, 93,  
 25 95, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, and 226.

Also provided are isolated polypeptide that are cell surface receptors that lack  
 30 at least part of a transmembrane domain such that the resulting polypeptide is not membrane localized or bound and it modulates an activity, including a biological

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activity, of the cell surface receptor. The polypeptides can include exon insertions. Among these are cell surface receptor isoforms selected from among isoforms of FGFR-4, KIT and TNFR. Exemplary of the isolated polypeptides are those that have at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity with a sequence of amino acids set forth in any of SEQ ID NOS: 91, 93, 95, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, and 226. Sequence identity is compared along the full length of each SEQ ID to the sequence of the full length of the isolated polypeptide. The isolated polypeptides can further lack a cell surface receptor cytoplasmic domain.

Also provided are isolated polypeptides that contain an intron-encoded sequence of amino acids and lack a cell surface receptor cytoplasmic domain. The intron is an intron and is selected from among nucleic acids KIT, FGFR-4, TNFR2, VEGFR-1, RON, TEK, Tie-1, and EphA1, or is an intron from any of SEQ ID NOS: 91, 93, 95, 121, 123, 129, 131, 133, 135, 137, 139, 141, 149, 151, or 153. Also provided are polypeptides that further lack a transmembrane domain. Among these are isolated polypeptides that modulate an activity or function of a cell surface receptor. These polypeptides include TNFR isoforms, such as, but not limited to, TNFR1, TNFR2 and TNFRp, the low-affinity nerve growth factor receptor, Fas antigen, CD40, CD27, CD30, 4-1BB, OX40, DR3, DR4, DR5, and herpes virus entry mediator (HVEM).

Also provided are chimeric intron fusion protein isoforms that contain an N-terminal portion that effects binding to a CSR linked to an intron, such as the intron or a portion thereof whereby the resulting chimera modulates, particularly, inhibits, an activity of one or more CSRs. The chimeras include N-terminal and/or intron portions of any of the isoforms provided herein and also a herstatin, linked to an intron from a different intron fusion protein isoform. The portions of the chimeras can be linked via a linker or via 2 or more amino acids. Alternatively, the chimera can be a chemical conjugate.



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Also provided are CSR isoforms conjugates and chimeras in which the N-terminal portion and intron-encoded portion are linked directly or via a linker and are from the same or a different CSR isoforms, including any provided herein, a herstatin or any other CSR. The two portions can be linked via a linker, such as a polypeptide or chemical linker. The isoform conjugates modulate, typically inhibit, the activity of one or more CSRs. The CSRs include those that participate in signal transduction, particularly CSRs involved in pathways that participate in angiogenesis, inflammatory responses and cell proliferation (see, *e.g.*, Figure 1).

Provided herein are CSR isoforms that contain at least one domain of a CSR receptor and lack one or more amino acids of another domain of the CSR receptor such as the transmembrane domain and/or protein kinase domain, whereby an activity is reduced or abolished compared to the CSR. CSR isoforms include polypeptides that contain an intron-encoded sequence of amino acids, wherein the intron is from a gene encoding the CSR. For example, a CSR isoform can contain at least one domain of the CSR receptor operatively linked to at least one amino acid encoded by an intron of a gene encoding the CSR. Among the CSR isoforms provided herein are polypeptides that contain one or more domains of an Ephrin (Eph) receptor, a fibroblast growth factor (FGF) receptor, a DDR receptor, a MET receptor, a RON receptor, a TEK/TIE receptor, a VEGF receptor, PDGF receptor, CSF1 receptor, a KIT receptor and a TNFR receptor.

Provided herein are EphA isoforms. The isoforms are isolated polypeptides that contain at least one domain of an EphA receptor. The polypeptides contain an ephrin ligand binding domain and lack one or more amino acids corresponding to the transmembrane domain of the EphA receptor, whereby the membrane localization of the polypeptide is reduced or abolished compared to the EphA receptor. Included are polypeptides where the EphA receptor is selected from among EphA1, EphA2, EphA3, EphA4, EphA5, EphA6, EphA7, and EphA8. In one example, such polypeptides include a sequence as set forth in any one of SEQ ID NO: 253 – 260 or an allelic variant thereof. The allelic variant can be an allelic variation present in any one of SEQ ID NOS: 289-293. EphA isoforms include polypeptides that lack all or

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part of a protein kinase domain compared to the EphA receptor and/or that lack all or part of a Sterile Alpha Motif domain (SAM) compared to the EphA receptor.

In one example, an EphA isoform has at least one domain of an EphA1 receptor as set forth in SEQ ID NO:253. Such isoforms include EphA1 isoforms  
5 where the polypeptide lacks one or more amino acids of a protein kinase domain of the EphA1 receptor, whereby the kinase activity of the polypeptide is reduced or abolished compared to the EphA1 receptor. EphA1 isoforms also include polypeptides that have at least 80% sequence identity with a sequence of amino acids set forth in any of SEQ ID NOS: 149, 151 and 153 or that contain the amino acid  
10 sequence set forth in any of SEQ ID NOS: 149, 151 and 153 or an allelic variant thereof. Allelic variants include the allelic variations as set forth in SEQ ID NO: 289. EphA1 isoforms include polypeptides that contain the same number of amino acids as set forth in any of SEQ ID NOS: 149, 151 and 153.

Provided herein are EphA2 isoforms. EphA2 isoforms include at least one  
15 domain of an EphA2 receptor as set forth in SEQ ID NO:254, where the polypeptide lacks one or more amino acids of a transmembrane domain and protein kinase domain compared to the EphA2 receptor, whereby the membrane localization and the protein kinase activity of the polypeptide are reduced or abolished compared to the EphA2 receptor. EphA2 isoforms include polypeptides that contain one or more amino acids  
20 of a fibronectin domain compared to the EphA2 receptor. Examples of EphA2 isoforms also include polypeptides that have at least 80% sequence identity with a sequence of amino acids as set forth in SEQ ID NO: 168 or contains the amino acid sequence set forth in SEQ ID NO: 168 or an allelic variant thereof. Allelic variants include, but are not limited to, allelic variations as set forth in SEQ ID NO: 290.  
25 EphA2 isoforms include isoforms that contain the same number of amino acids as set forth in the SEQ ID NO:168.

Also provided herein are EphB isoforms that include polypeptides lacking one or more amino acids of a transmembrane domain compared to the EphB receptor, whereby the membrane localization of the polypeptide is reduced or abolished  
30 compared to the EphB receptor. Among the EphB isoforms provided are those where the EphB receptor is selected from EphB1, EphB2, EphB3, EphB4, EphB5, and

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EphB6 and where the EphB receptor comprises a sequence as set forth in any one of SEQ ID NOS: 261-265 or an allelic variant thereof. Allelic variants include, but are not limited to, allelic variations set forth in SEQ ID NOS: 294-298. Exemplary EphB isoforms include isoforms that lack one or more amino acids of a protein kinase domain of the EphB receptor, whereby the protein kinase activity of the polypeptide is reduced or abolished compared to the EphB receptor and isoforms that lacks one or more amino acids of a Sterile Alpha Motif domain (SAM) of the EphB receptor. In one example, an EphB1 isoform includes an ephrin binding domain. EphB isoforms also include isoforms that lack one or more amino acids of a fibronectin domain of the EphB receptor. Among the EphB isoforms provided herein are isoforms that have at least 80% sequence identity with a sequence of amino acids as set forth in any of SEQ ID NOS: 155, 170, 172 and 174 and isoforms that contain the amino acid sequence as set forth in any of SEQ ID NOS: 155, 170, 172 and 174 or an allelic variant thereof. Allelic variants include, but are not limited to, allelic variations set forth in SEQ ID NOS: 294 and 297. EphB isoforms include isoforms that contain the same number of amino acids as set forth in any of SEQ ID NOS: 155, 170, 172 and 174.

FGFR isoforms are provided herein. Included are FGFR isoforms that contain at least one domain of an FGFR-1, wherein the polypeptide comprises an immunoglobulin domain corresponding to amino acids 253 – 357 of FGFR-1 set forth in SEQ ID NO:268 and lacks all of a transmembrane domain corresponding to amino acids 375 – 397 of the FGFR-1. FGFR isoforms also include isoforms that lack one or more amino acids of a protein kinase domain of FGFR-1, whereby the protein kinase activity of the polypeptide is reduced or abolished compared to the FGFR-1 and/or that contain one or more amino acids of an immunoglobulin domain corresponding to amino acids 156 – 246 of FGFR-1. FGFR isoforms provided include isoforms that have at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NOS: 119 or 176 and isoforms that contain any of SEQ ID NOS: 119 and 176 or an allelic variant thereof. Allelic variants include, but are not limited to, allelic variations set forth in SEQ ID NO: 300. FGFR-1 isoforms include isoforms that have the same number of amino acids as set forth in any of SEQ ID NOS: 119 and 176.

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Also provided are FGFR-2 isoforms that have at least one domain of an FGFR-2 as set forth in SEQ ID NO: 269, where the polypeptide lacks a transmembrane domain and a protein kinase domain compared to FGFR-2, whereby the membrane localization and protein kinase activity of the polypeptide is reduced or abolished compared to FGFR-2. Such isoforms include polypeptides that have at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NOS: 178, 180, 182 and 184 and isoforms that contain the amino acid sequence set forth in SEQ ID NOS: 178, 180, 182 or 184 or an allelic variant thereof. Allelic variants include, but are not limited to, allelic variations set forth in SEQ ID NO: 301. FGFR-2 isoforms include isoforms that have the same number of amino acids as set forth in any of SEQ ID NOS: 178, 180, 182 or 184. Exemplary FGFR-2 isoforms also include isoforms that lack an immunoglobulin domain corresponding to amino acids 41-125 of the FGFR-2.

FGFR-4 isoforms are provided herein that contain at least one domain of an FGFR-4, such as an immunoglobulin domain corresponding to amino acids 249 – 351 of the FGFR-4 set forth in SEQ ID NO: 271 and lack a transmembrane domain and protein kinase domain of the FGFR-4, whereby the membrane localization and protein kinase activity of the polypeptide is reduced or abolished compared to FGFR-4. FGFR isoforms include isoforms that have at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NO: 121 and isoforms that contain the amino acid sequence set forth in SEQ ID NO: 121 or an allelic variant thereof. Allelic variants include, but are not limited to, allelic variations set forth in SEQ ID NO: 303. FGFR-4 isoforms include isoforms that have the same number of amino acids as set forth in SEQ ID NO: 121.

Provided herein are DDR1 isoforms, that are polypeptides that contain at least one domain of a DDR1 as set forth in SEQ ID NO: 250, where the polypeptide lacks a transmembrane domain and a protein kinase domain compared to the DDR1, whereby the membrane localization and protein kinase activity of the polypeptide is reduced or abolished compared to DDR1, and the polypeptide has at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NOS: 115 or 117. DDR1 isoforms include isoforms that contain the amino acid sequence set forth in SEQ ID

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NOS: 115 or 117 or an allelic variant thereof, such as but not limited to the allelic variations as set forth in SEQ ID NO: 286. DDR1 isoforms include isoforms that have the same number of amino acids as set forth in SEQ ID NOS: 115 or 117.

Also provided herein are MET receptor isoforms that are polypeptides which  
5 contain at least one domain of a MET receptor operatively linked to at least one amino acid encoded by an intron of a gene encoding MET, where the polypeptide lacks a transmembrane domain, protein kinase domain and at least one additional domain compared to a MET receptor set forth in SEQ ID NO:274, whereby the membrane localization and protein kinase activity of the polypeptide is reduced or  
10 abolished compared to the MET receptor. MET receptor isoforms include isoforms where the additional domain lacking as compared to the MET receptor is a Sema domain, a plexin domain or an IPTG/TIG domain. MET receptor isoforms include isoforms that have at least 80% sequence identity with a sequence of amino acids as set forth in any of SEQ ID NOS: 186, 188, 190, 192, 196, 198, 200, 202, 204, 206,  
15 208 and 214 and isoforms that contain the amino acid sequence set forth in any of SEQ ID NOS: 186, 188, 190, 192, 196, 198, 200, 202, 204, 206, 208 and 214 or an allelic variant thereof. Allelic variants include, but are not limited to, allelic variations set forth in SEQ ID NO: 306. MET isoforms include isoforms that have the same number of amino acids as set forth in any of SEQ ID NOS: 186, 188, 190, 192,  
20 196, 198, 200, 202, 204, 206, 208 and 214.

RON receptor isoforms are provided herein. RON receptor isoforms include polypeptides that have a plexin domain of the RON receptor as set forth in SEQ ID NO: 277; and lack a transmembrane domain of the RON receptor, whereby the membrane localization of the polypeptide is reduced or abolished compared to the  
25 RON receptor. RON receptor isoforms include isoforms that lack one or more amino acids of a protein kinase domain compared to the RON receptor as set forth in SEQ ID NO: 277, whereby the protein kinase activity of the polypeptide is reduced or abolished compared to the RON receptor and/or contain one or more amino acids of at least one IPTG/TIG domain of the RON receptor. RON receptor isoforms include  
30 isoforms that have at least 80% sequence identity with a sequence of amino acids as set forth in any of SEQ ID NOS: 216, 218 and 220 and isoforms that contain the

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amino acid sequence set forth in any of SEQ ID NOS: 216, 218 and 220 or an allelic variant thereof, such as but not limited to allelic variations set forth in SEQ ID NO: 308. RON receptor isoforms also include isoforms that have the same number of amino acids as set forth in any of SEQ ID NOS: 216, 218 and 220.

5            Provided herein are TEK isoforms that contain at least one domain of a TEK receptor as set forth in SEQ ID NO: 278, where the isoform lacks a transmembrane domain, and a protein kinase domain, whereby the membrane localization and protein kinase activity of the polypeptide are reduced or abolished compared to the TEK receptor; and lacks one or more amino acids of at least one fibronectin domain  
10 compared to the TEK receptor. TEK isoforms include isoforms where the fibronectin domain lacking corresponds to amino acids 444 – 529, 543 – 626, or 639 – 724 of SEQ ID NO: 278 and where one or more amino acids of the three fibronectin domains of the TEK receptor corresponding to amino acids 444 – 529, 543 – 626, and 639 – 724 of SEQ ID NO: 278 is lacking. TEK isoforms include isoforms that have at  
15 least 80% sequence identity with a sequence of amino acids as set forth in any of SEQ ID NOS: 131 and 133 and isoforms that contain the amino acid sequence set forth in any of SEQ ID NOS: 131 and 133 or an allelic variant thereof, such as but not limited to allelic variations as set forth in SEQ ID NO: 309. Tek isoforms also include isoforms that contain the same number of amino acids as set forth in any of SEQ ID  
20 NOS: 131 and 133.

            Tie receptor isoforms are provided herein that contain all or part of at least one domain of a Tie-1 receptor as set forth in SEQ ID NO: 279, where the isoform lacks a transmembrane domain and a protein kinase domain compared to the Tie-1 receptor, whereby the membrane localization and protein kinase activity of the polypeptide are  
25 reduced or abolished compared to the Tie-1 receptor; and the isoform contains an amino acid sequence as set forth in any of SEQ ID NOS: 135, 137, 139, 141, 143 and 222 or an allelic variant thereof. Allelic variants include, but are not limited to, allelic variations set forth in SEQ ID NO: 310. Tie receptor isoforms include isoforms that have the same number of amino acids as set forth in any of SEQ ID NOS: 135, 137,  
30 139, 141, 143 and 222.

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Provided herein are VEGFR isoforms. VEGFR isoforms include VEGFR-1 isoforms that contain a sequence of amino acids that has at least 80% sequence identity with the sequence of amino acids as set forth in SEQ ID NO:123 and that lack a transmembrane domain and a protein kinase domain compared to the VEGFR-1 receptor set forth in SEQ ID NO: 282. Such isoforms include polypeptides that contain the amino acid sequence set forth in SEQ ID NO: 123 or an allelic variant thereof and isoforms that contain the same number of amino acids as set forth in any of SEQ ID NO: 123. VEGFR isoforms include VEGFR-2 and VEGFR-3 isoforms that contain at least one domain of a VEGFR set forth in any of SEQ ID NOS:283 and 284, where the polypeptide lacks one or more amino acids of a transmembrane domain of the VEGFR, whereby the membrane localization of the polypeptide is reduced or abolished compared to the VEGFR. VEGFR-2 and VEGFR-3 isoforms also include isoforms that lack one or more amino acids of a protein kinase domain, whereby the protein kinase activity of the polypeptide is reduced or abolished compared to the VEGFR and isoforms that lack one or more amino acids of an immunoglobulin domain compared to the VEGFR. VEGFR-2 and VEGFR-3 isoforms include polypeptides that have at least 80% sequence identity with a sequence of amino acids as set forth in any of SEQ ID NOS: 125, 127, 224 and 226 and polypeptides that contain the amino acid sequence set forth in any of SEQ ID NOS: 125, 127, 224 and 226 or an allelic variant thereof. Allelic variants can include, but are not limited to the allelic variations as set forth in SEQ ID NO: 313 and 314. VEGFR-2 and VEGFR-3 isoforms also include isoforms that have the same number of amino acids as set forth in any of SEQ ID NOS: 125, 127, 224 and 226.

PDGFR isoforms are provided herein. Included are PDGFR isoforms that contain at least one domain of a PDGFR-B as set forth in SEQ ID NO: 276, wherein the polypeptide lacks one or more amino acids of a transmembrane domain of the PDGFR-B, whereby the membrane localization of the polypeptide is reduced or abolished compared to the PDGFR-B. PDGFR isoforms also include isoforms that lack one or more amino acids of a protein kinase domain of the PDGFR-B, whereby the protein kinase activity of the polypeptide is reduced or abolished compared to the PDGFR-B and isoforms that contain one or more amino acids of an immunoglobulin

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domain of the PDGFR-B. Also included are PDGFR isoforms that have at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NO: 147 and isoforms that contain the amino acid sequence set forth in SEQ ID NO: 147 or an allelic variant thereof. Allelic variants can include, but are not limited to the allelic variations as set forth in SEQ ID NO: 307. PDGFR isoforms also include isoforms that have the same number of amino acids as set forth in SEQ ID NO: 147.

Also provided herein are CSF1R isoforms that contain at least one domain of a CSF1R as set forth in SEQ ID NO: 249, where the polypeptide lacks one or more amino acids of a transmembrane domain of the CSF1R, whereby the membrane localization of the polypeptide is reduced or abolished compared to the CSF1R. CSF1R isoforms also include isoforms that lack one or more amino acids of a protein kinase domain of the CSF1R, whereby the protein kinase activity of the polypeptide is reduced or abolished compared to the CSF1R and isoforms that contain one or more amino acids of an immunoglobulin domain of the CSF1R. Included are CSF1R isoforms that have at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NOS: 145 and isoforms that contain the amino acid sequence set forth in SEQ ID NOS: 145 or an allelic variant thereof, such as but not limited to allelic variations as set forth in SEQ ID NO: 285. Exemplary CSF1R isoforms also include isoforms that contain the same number of amino acids as set forth in SEQ ID NO: 145.

KIT receptor isoforms are provided herein. Included are KIT receptor isoforms that contain at least one domain of a KIT receptor as set forth in SEQ ID NO:273 and lack one or more amino acids of a transmembrane domain and a protein kinase domain of the KIT receptor, whereby the membrane localization and protein kinase activity of the polypeptide are reduced or abolished compared to the KIT receptor and isoforms that contain at least one immunoglobulin domain of the KIT receptor. KIT isoforms include isoforms that have at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NOS: 93 and isoforms that contain the amino acid sequence set forth in SEQ ID NO: 93 or an allelic variant thereof, such as but not limited to the allelic variations as set forth in SEQ ID NO:



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305. KIT receptor isoforms include isoforms that have the same number of amino acids as set forth in SEQ ID NO: 93.

Provided herein are TNFR isoforms that contain at least one cysteine rich c6 domain of a TNFR as set forth in SEQ ID NOS:280 or 281 and lack all of the  
5 transmembrane domain of the TNFR, whereby the membrane localization of the polypeptide is reduced or abolished compared to the TNFR. TNFR isoforms include isoforms that contain at least two cysteine rich c6 domains of the TNFR. TNFR isoforms also include isoforms that have at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NO: 95 and isoforms that contain the  
10 sequence set forth in SEQ ID NO: 95 or an allelic variant thereof. Allelic variation includes but is not limited to allelic variations as set forth in SEQ ID NO: 312. TNFR isoforms also include isoforms that have the same number of amino acids as set forth in SEQ ID NO: 95.

The isolated polypeptides (e.g, CSR isoforms) can be encoded by a gene in a  
15 mammal, particularly a human, and can be isolated from a mammalian cell or prepared from nucleic acid cloned from such cell or can be synthesized from nucleic acid prepared by any means or can be synthesized as polypeptides. Exemplary mammals include humans and other primates, horses, cattle, dogs, cats and other domesticated animals, and rodents, such as rats and mice. The isolated polypeptides  
20 can be identified by the methods provided herein, known to those of skill in the art and/ or also in, for example, copending application U.S. application Serial No. 10/846,113 and published PCT application No. WO 2005/016966.

Also provided are pharmaceutical compositions that contain any of the isolated polypeptides or combinations thereof. Included among the compositions are  
25 those that contain a polypeptide that complexes with a receptor tyrosine kinase or a tumor necrosis factor receptor. The pharmaceutical compositions can be used to treat diseases that include inflammatory diseases, immune diseases, cancers, and other diseases that manifest aberrant angiogenesis or neovascularization or cell proliferation. Cancers include breast, lung, colon, gastric cancers, pancreatic cancers  
30 and others. Inflammatory diseases, include, for example, diabetic retinopathies and/or neuropathies and other inflammatory vascular complications of diabetes,

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autoimmune diseases, including autoimmune diabetes, atherosclerosis, Crohn's disease, diabetic kidney disease, cystic fibrosis, endometriosis, diabetes-induced vascular injury, inflammatory bowel disease, Alzheimer's disease and other neurodegenerative diseases, and other diseases known to those of skill in the art that  
5 involve proliferative responses, immune responses and inflammatory responses and others in which RTKs, particularly those noted in Figure 1 and throughout the disclosure herein are implicated, involved or in which they participate.

Also provided are nucleic acid molecules encoding any of the polypeptides. Vectors containing the nucleic acid molecules are provided as are cells containing the  
10 vectors or nucleic acid molecules. Among the nucleic acid molecules provided are those that contain an intron and an exon, where the intron contains a stop codon; the nucleic acid molecule encodes an open reading frame that spans an exon intron junction; and the open reading frame terminates at the stop codon in the intron. The intron can encode one or more amino acids of the encoded polypeptide or the codon  
15 can be a first codon (and possibly the only codon) in the intron.

Also provided are nucleic acid molecules that contain a sequence of nucleotides that has at least 90% sequence identity with a sequence of nucleotides set forth in any of SEQ ID NOS: 90, 92, 94, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 167, 169, 171, 173, 175,  
20 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, and 225 or an allelic variant thereof. Sequence identity is compared along the full length of each SEQ ID to the full length sequence of the isolated nucleic acid molecule, and each of SEQ ID NOS: 90, 92, 94, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150,  
25 152, 154, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, and 225 is a cell surface receptor isoform. In particular, nucleic acid molecules containing the sequence of nucleotides set forth in any of SEQ ID NOS: 90, 92, 94, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152,  
30 154, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, and 225 are

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provided. Also provided are vectors containing any of the nucleic acid molecules and cells containing the nucleic acid molecules or vectors.

Pharmaceutical compositions containing the nucleic acid molecules and/or vectors are provided. Such compositions can be used in methods of gene therapy,  
5 including *in vivo* methods and *ex vivo* methods.

Methods of treating a disease or condition by administering any of the pharmaceutical compositions are provided. Diseases or conditions include, but are not limited to, for example, cancers, inflammatory diseases, infectious diseases, angiogenic-related conditions, other cell proliferative conditions, immune disorders  
10 and neurodegenerative diseases. Also included are methods of treatment where the pharmaceutical compositions contain one or more polypeptides that inhibit(s) angiogenesis, cell proliferation, cell migration, viral entry, viral infection, tumor cell growth or tumor cell metastasis.

Exemplary of diseases and disorders are any of rheumatoid arthritis, multiple  
15 sclerosis and posterior intraocular inflammation, uveitic disorders, ocular surface inflammatory disorders, neovascular disease, proliferative vitreoretinopathy, atherosclerosis, endometriosis, rheumatoid arthritis, hemangioma, diabetes mellitus, diabetic retinopathies, inflammatory bowel disease, Crohn's disease, psoriasis, Alzheimer's disease, lupus, vascular stenosis, restenosis, inflammatory joint disease,  
20 atherosclerosis, urinary obstructive syndromes, asthma, carcinoma, lymphoma, blastoma, sarcoma, and leukemia, lymphoid malignancies, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric cancer, stomach cancer, gastrointestinal cancer, pancreatic cancer,  
25 glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney/renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, and head and neck cancer and other cancers. Other diseases or conditions include those  
30 caused by or mediated by or involving a virus or a parasite, such as, but not limited to, Myxoma virus, Vaccinia virus, Tanapox virus, Epstein-Barr virus, Herpes simplex

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virus, Cytomegalovirus, Herpesvirus saimiri, Hepatitis B virus, African swine fever virus, Parovirus, Human Immune deficiency virus (HIV), Hepatitis C virus, Influenza virus, Respiratory syncytial virus, Measles virus, Vesicular stomatitis virus, Dengue virus and Ebola virus.

5           Also provided are combinations and kits containing the combinations, with optional instructions and/or reagents. These combinations contain compositions that contain two and one or more different cell surface receptor isoforms and/or a therapeutic drug or a cell surface receptor isoform and a therapeutic drug. The isoforms and/or drugs can be in separate compositions or in a single composition or  
10   one composition containing two or more of the agents and the other containing the other agents or other such formal. Methods of treatment by administering the components of the combination are provided. Each component can be administered separately, simultaneously, intermittently, in a single composition or combinations thereof.

## 15   **BRIEF DESCRIPTION OF THE FIGURE**

**Figure 1** depicts angiogenic and endothelial cell maintenance pathways. Target points for CSR isoform modulation of one or more pathway steps are indicated. In particular, the figure depicts steps in the formation, maintenance and remodeling of the vasculature. These include the role(s) of VEGF's in recruitment of circulating  
20   endothelial precursors (CEPs), the roles of angioipoinetin-2 in vessel destabilization.

### **DETAILED DESCRIPTION**

#### **A.   Definitions**

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the  
25   invention(s) belong. All patents, patent applications, published applications and publications, GENBANK sequences, websites and other published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their entirety. In the event that there is a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such  
30   identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information is known and

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can be readily accessed, such as by searching the internet and/or appropriate databases. Reference thereto evidences the availability and public dissemination of such information.

As used herein, a cell surface receptor (CSR) is a protein that is expressed on the surface of a cell and typically includes a transmembrane domain or other moiety that anchors it to the surface of a cell. As a receptor it binds to ligands that mediate or participate in an activity of the cell surface receptor, such as signal transduction or ligand internalization. Cell surface receptors include, but are not limited to, single transmembrane receptors and G-protein coupled receptors. Receptor tyrosine kinases, such as growth factor receptors, also are among such cell surface receptors.

As used herein, a receptor tyrosine kinase (RTK) refers to a protein, typically a glycoprotein, that is a member of the growth factor receptor family of proteins. Growth factor receptors are typically involved in cellular processes including cell growth, cell division, differentiation, metabolism and cell migration. RTKs also are known to be involved in cell proliferation, differentiation and determination of cell fate as well as tumor growth. RTKs have a conserved domain structure including an extracellular domain, a membrane-spanning (transmembrane) domain and an intracellular tyrosine kinase domain. Typically, the extracellular domain binds to a polypeptide growth factor or a cell membrane-associated molecule or other ligand. The tyrosine kinase domain is involved in positive and negative regulation of the receptor.

Receptor tyrosine kinases are grouped into families based on, for example, structural arrangements of sequence motifs in their extracellular domains. Structural motifs include, but are not limited to repeats of regions of: immunoglobulin, fibronectin, cadherin, epidermal growth factor and kringle repeats. Classification by structural motifs has identified greater than 16 families of RTKs, each with a conserved tyrosine kinase domain. Examples of RTKs include, but are not limited to, erythropoietin-producing hepatocellular (EPH) receptors, epidermal growth factor (EGF) receptors, fibroblast growth factor (FGF) receptors, platelet-derived growth factor (PDGF) receptors, vascular endothelial growth factor (VEGF) receptor, cell adhesion RTKs (CAKs), Tie/Tek receptors, insulin-like growth factor (IGF)

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receptors, and insulin receptor related (IRR) receptors. Exemplary genes encoding RTKs include, but are not limited to, ErbB2, ErbB3, DDR1, DDR2, EGFR, EphA1, EphA8, FGFR-2, FGFR-4, Flt1 (fms-related tyrosine kinase 1 receptor; also known as VEGFR-1), FLK1 (also known as VEGFR-2), MET, PDGFR-A, PDGFR-B, and TEK  
5 (also known as TIE-2).

Dimerization of RTKs activates the catalytic tyrosine kinase domain of the receptor and tyrosine autophosphorylation. Autophosphorylation in the kinase domain maintains the tyrosine kinase domain in an activated state. Autophosphorylation in other regions of the protein influences interactions of the receptor with other  
10 cellular proteins. In some RTKs, ligand binding to the extracellular domain leads to dimerization of the receptor. In some RTKs, the receptor can dimerize in the absence of ligand. Dimerization also can be increased by receptor overexpression.

As used herein, a tumor necrosis factor receptor (TNFR) refers to a member of a family of receptors that have a characteristic repeating extracellular cysteine-rich  
15 motif such as found in TNFR1 and TNFR2. TNFRs also have a variable intracellular domain that differs between members of the TNFR family. The TNFR family of receptors includes, but is not limited to, TNFR1, TNFR2, TNFRp, the low-affinity nerve growth factor receptor, Fas antigen, CD40, CD27, CD30, 4-1BB, OX40, DR3, DR4, DR5, and herpesvirus entry mediator (HVEM). Ligands for TNFRs include  
20 TNF-  $\alpha$ , lymphotoxin, nerve growth factor, Fas ligand, CD40 ligand, CD27 ligand, CD30 ligand, 4-1BB ligand, OX40 ligand, APO3 ligand, TRAIL and LIGHT. TNFRs include an extracellular domain, including a ligand binding domain, a transmembrane domain and an intracellular domain that participates in signal transduction. TNFRs are typically trimeric proteins that trimerize at the cell surface.

25 As used herein, an isoform of a cell surface receptor (also referred to herein as a CSR isoform), such as an isoform of a receptor tyrosine kinase, refers to a receptor that lacks a domain or portion thereof sufficient to alter an activity of the receptor or modulate an activity compared to a wildtype and/or predominant form of the receptor or lacks a structural feature, such as a domain. Thus, a CSR isoform refers to a  
30 receptor that lacks a domain or portion of a domain sufficient to alter an activity, typically a biological activity, of the receptor. A CSR isoform lacks a domain or

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portion of a domain sufficient to alter or modulate an activity of the receptor. A CSR isoform can include an isoform that has one or more biological activities that are altered from the receptor; for example, an isoform can include the alteration of the extracellular domain of p185-HER2, altering the isoform from a positively acting regulatory polypeptide of the receptor to a negatively acting regulatory polypeptide of the isoform, *e.g.* from a receptor domain into a ligand. Generally, an activity is altered in an isoform at least 0.1, 0.5, 1, 2, 3, 4, 5, or 10 fold compared to a wildtype and/or predominant form of the receptor. Typically, a activity is altered by at 2, 5, 10, 20, 50, 100 or 1000 fold or more. In one embodiment, alteration of an activity is a reduction in the activity. With reference to an isoform, alteration of activity refers to difference in activity between the particular isoform, which is shortened, compared to the unshortened form of the receptor. Alteration of an activity includes an enhancement or a reduction of activity. In one embodiment, an alteration of an activity is a reduction in biological activity; the reduction can be at least 0.1 0.5 1, 2, 3, 4, 5, or 10 fold compared to a wildtype and/or predominant form of the receptor. Typically, a biological activity is reduced 5, 10, 20, 50, 100 or 1000 fold or more.

As used herein, reference to modulating the activity of a cell surface receptor means that a CSR interacts in some manner with the receptor and activity, such as ligand binding or dimerization or other signal-transduction-related activity is altered.

As used herein, reference to a CSR isoform with altered activity refers to an alteration in an activity by virtue of the different structure or sequence of the CSR isoform compared to a cognate receptor.

As used herein, an intron fusion protein refers to an isoform that lacks one or more domain(s) or portion of one or more domain(s) resulting in an alteration of an activity of a receptor. The activity can be altered by the intron fusion protein directly, such as by interaction with the receptor, or indirectly by interacting with a receptor ligand or co-factor or other modulator of receptor activity. Intron fusion proteins isolated from cells or tissues or that have the sequence of such polypeptides isolated from cells or tissues, are "natural." Those that do not occur naturally but that are synthesized or prepared by linking a molecule to an intron such that the resulting

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construct modulates the activity of a CSR are "synthetic." Included among intron fusion proteins are cell surface receptor isoforms that lack one or more domain(s) or portion of one or more domain(s) resulting in an alteration of an activity of a receptor. In addition, an intron fusion protein contains one or more amino acids not encoded by an exon (with reference to the predominant or wildtype form of a receptor), operatively linked to exon-encoded amino acids. Generally such isoforms are shortened compared to a wildtype or predominant form encoded by a CSR gene. They, however, can include insertions or other modifications in the exon portion and, thus, be of the same size or larger than the predominant form. Each, however, includes an intron-encoded portion (at least one amino acid, generally at least, 2, 3, 4, 5, 8, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75 and more amino acids). An intron fusion protein can be encoded by an alternatively spliced RNA and/or RNA molecules identified *in silico* by identifying potential splice sites and then producing such molecules by recombinant methods. Typically, an intron fusion protein is shortened by the presence of one or more stop codons in an intron fusion protein-encoding RNA that are not present in the corresponding sequence of an RNA encoding a wildtype or predominant form of a CSR polypeptide. Addition of amino acids and/or a stop codon can result in an intron fusion protein that differs in size and sequence from a wildtype or predominant form of a polypeptide.

Intron fusion proteins for purposes herein include natural combinatorial and synthetic intron fusion proteins. A natural intron fusion protein refers to a polypeptide that is encoded by an alternatively spliced RNA molecule that contains one or more amino acids encoded by an intron linked to one or more portions of the polypeptide encoded by one or more exons of a gene. Alternatively spliced mRNA is isolated or can be prepared synthetically by joining splice donor and acceptor sites in a gene. A natural intron fusion protein contains one or more amino acids and/or a stop codon encoded by an intron sequence and generally occurs in cells and/or tissues, but can be identified from a gene by identifying splice donor and acceptor sites and identifying possible encoded spliced variants. A combinatorial intron fusion protein refers to a polypeptide that is shortened compared to a wildtype or predominant form



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of a polypeptide. Typically, the shortening removes one or more domains or a portion thereof from a polypeptide such that an activity is altered. Combinatorial intron fusion proteins often mimic a natural intron fusion protein in that one or more domains or a portion thereof that is/are deleted in a natural intron fusion protein  
5 derived from the same gene or derived from a gene in a related gene family. Those that do not occur naturally but that are synthesized or prepared by linking a molecule to an intron such that the resulting construct modulates the activity of a CSR are "synthetic."

As used herein, natural with reference to intron fusion protein, refers to any  
10 protein, polypeptide or peptide or fragment thereof (by virtue of the presence of the appropriate splice acceptor/donor sites) that is encoded within the genome of an animal and/or is produced or generated in an animal or that could be produced from a gene. Natural intron fusion proteins include allelic variants. Intron fusion proteins can be modified post-translationally.

As used herein, an exon refers to a nucleic acid molecule containing  
15 sequence of nucleotides that is transcribed into RNA and is represented in a mature form of RNA, such as mRNA (messenger RNA), after splicing and other RNA processing. An mRNA contains one or more exons operatively linked. Exons can encode polypeptides or a portion of a polypeptide. Exons also can contain non-  
20 translated sequences for example, translational regulatory sequences. Exon sequences are often conserved and exhibit homology among gene family members.

As used herein, an intron refers to a sequence of nucleotides that is transcribed into RNA and is then typically removed from the RNA by splicing to create a mature form of an RNA, for example, an mRNA. Typically, nucleotide sequences of introns  
25 are not incorporated into mature RNAs, nor are intron sequences or a portion thereof typically translated and incorporated into a polypeptide. Splice signal sequences such as splice donors and acceptors are used by the splicing machinery of a cell to remove introns from RNA. It is noteworthy that an intron in one splice variant can be an exon (i.e., present in the spliced transcript) in another variant. Hence, spliced mRNA  
30 encoding an intron fusion protein can include an exon(s) and introns.

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As used herein, splicing refers to a process of RNA maturation where introns in the mRNA are removed and exons are operatively linked to create a messenger RNA (mRNA).

As used herein, alternative splicing refers to the process of producing multiple mRNAs from a gene. Alternate splicing can include operatively linking less than all the exons of a gene, and/or operatively linking one or more alternate exons that are not present in all transcripts derived from a gene.

As used herein, exon deletion refers to an event of alternative RNA splicing that produces a nucleic acid molecule that lacks at least one exon compared to an RNA molecule encoding a wildtype or predominant form of a polypeptide. An RNA molecule that has a deleted exon can be produced by such alternative splicing or by any other method, such as an *in vitro* method to delete the exon.

As used herein, exon insertion, refers to an event of alternative RNA splicing that produces a nucleic acid molecule that contains at least one exon not typically present in an RNA molecule encoding a wildtype or predominant form of a polypeptide. An RNA molecule that has an inserted exon can be produced by such alternative splicing or by any other method, such as an *in vitro* method to add or insert the exon.

As used herein, exon extension refers to an event of alternative RNA splicing that produces a nucleic acid molecule that contains at least one exon that is greater in length (number of nucleotides contained in the exon) than the corresponding exon in an RNA encoding a wildtype or predominant form of a polypeptide. An RNA molecule that has an extended exon can be produced by such alternative splicing or by any other method, such as an *in vitro* method to extend the exon. In some instances, as described herein, an mRNA produced by exon extension encodes an intron fusion protein.

As used herein, exon truncation refers to an event of alternative RNA splicing that produces a nucleic acid molecule that contains a truncation or shortening of one or more exons such that the one or more exons are shorter in length (number of nucleotides) compared to a corresponding exon in an RNA molecule encoding a wildtype or predominant form of a polypeptide. An RNA molecule that has a

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truncated exon can be produced by such alternative splicing or by any other method, such as an *in vitro* method to truncate the exon.

As used herein intron retention refers to an event of alternative RNA splicing that produces a nucleic acid molecule that contains an intron or a portion thereof  
5 operatively linked to one or more exons. An RNA molecule that retains an intron or portion thereof can be produced by such alternative splicing or by any other method, such as *in vitro* method to produce an RNA molecule with a retained exon. In some cases, as described herein, an mRNA molecule produced by intron retention encodes an intron fusion protein.

10 As used herein, a gene, also referred to as a gene sequence, refers to a sequence of nucleotides transcribed into RNA (introns and exons), including nucleotide sequence that encodes at least one polypeptide. A gene includes sequences of nucleotides that regulate transcription and processing of RNA. A gene also includes regulatory sequences of nucleotides such as promoters and enhancers, and  
15 translation regulation sequences.

As used herein, a splice site refers to one or more nucleotides within the gene that participate in the removal of an intron and/or the joining of an exon. Splice sites include splice acceptor sites and splice donor sites.

As used herein, cognate receptor with reference to the isoforms provided  
20 herein refers to the receptor that is encoded by the same gene as the particular isoform. Generally, the cognate receptor also is a predominant form in a particular cell or tissue. For example, herstatin is encoded by a splice variant of the pre-mRNA which encodes p185-HER2 (ErbB2 receptor). Thus, p185-HER2 is the cognate receptor for herstatin.

25 As used herein, a wildtype form, for example, a wildtype form of a polypeptide, refers to a polypeptide that is encoded by a gene. Typically a wildtype form refers to a gene (or RNA or protein derived therefrom) without mutations or other modifications that alter function or structure; wildtype forms include allelic variation among and between species.

30 As used herein, a predominant form, for example, a predominant form of a polypeptide, refers to a polypeptide that is the major polypeptide produced from a

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gene. A “predominant form” varies from source to source. For example, different cells or tissue types can produce different forms of polypeptides, for example, by alternative splicing and/or by alternative protein processing. In each cell or tissue type, a different polypeptide can be a “predominant form.”

5           As used herein, a domain refers to a portion (typically a sequence of three or more, generally 5 or 7 or more amino acids) of a polypeptide chain that can form an independently folded structure within a protein made up of one or more structural motifs (e.g. combinations of alpha helices and/or beta strands connected by loop regions) and/or that is recognized by virtue of a functional activity, such as kinase  
10 activity. A protein can have one, or more than one, distinct domain. For example, a domain can be identified, defined or distinguished by homology of the sequence therein to related family members, such as homology and motifs that define an extracellular domain. In another example, a domain can be distinguished by its function, such as by enzymatic activity, *e.g.* kinase activity, or an ability to interact  
15 with a biomolecule, such as DNA binding, ligand binding, and dimerization. A domain independently can exhibit a biological function or activity such that the domain independently or fused to another molecule can perform an activity, such as, for example proteolytic activity or ligand binding. A domain can be a linear sequence of amino acids or a non-linear sequence of amino acids from the polypeptide. Many  
20 polypeptides contain a plurality of domains. For example, receptor tyrosine kinases typically include, an extracellular domain, a membrane-spanning (transmembrane) domain and an intracellular tyrosine kinase domain.

          As used herein, a polypeptide lacking all or a portion of a domain refers a polypeptide that has a deletion of one or more amino acids or all of the amino acids of  
25 a domain compared to a cognate polypeptide. Amino acids deleted in a polypeptide lacking all or part of a domain need not be contiguous amino acids within the domain of the cognate polypeptide. Polypeptides that lack all or a part of a domain can include the loss or reduction of an activity of the polypeptide compared to the activity of a cognate polypeptide or loss of a structure in the polypeptide.

30           For example, if a cognate receptor has a transmembrane domain, then a receptor isoform polypeptide lacking all or a part of the transmembrane domain can

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have a deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more amino acids between amino acids corresponding to the same amino acid positions in the cognate receptor.

As used herein, a polypeptide that contains a domain refers to a polypeptide  
5 that contains a complete domain with reference to the corresponding domain of a cognate receptor. A complete domain is determined with reference to the definition of that particular domain within a cognate polypeptide. For example, a receptor isoform comprising a domain refers to an isoform that contains a domain  
10 corresponding to the complete domain as found in the cognate receptor. If a cognate receptor, for example, contains a transmembrane domain of 21 amino acids between amino acid positions 400-420, then a receptor isoform that comprises such transmembrane domain, contains a 21 amino acid domain that has substantial identity  
15 with the 21 amino acid domain of the cognate receptor. Substantial identity refers to a domain that can contain allelic variation and conservative substitutions as compared to the domain of the cognate receptor. Domains that are substantially identical do not have deletions, non-conservative substitutions or insertions of amino acids compared to the domain of the cognate receptor. Domains (*i.e.*, a furin domain, an Ig-like domain) often are identified by virtue of structural and/or sequence homology to domains in particular proteins.

20 Such domains are known to those of skill in the art who can identify such. For exemplification herein, definitions are provided, but it is understood that it is well within the skill in the art to recognize particular domains by name. If needed appropriate software can be employed to identify domains.

As used herein, an extracellular domain is a portion of the cell surface  
25 receptor that occurs on the surface of the receptor and includes the ligand binding site(s). In one example, an ephrin receptor ligand binding domain (EPH\_lbd) is the portion of the polypeptide that mediates binding of a protein receptor to an ephrin ligand. Typically, EphA receptors bind to GPI-anchored ephrin-A ligands, while EphB receptors bind to ephrin-B proteins that have a transmembrane and cytoplasmic  
30 domain.

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A Receptor L domain (RLD), such as for example in ErbB2, is another example of a domain that includes a ligand binding site. Each L domain contains a single-stranded right hand beta-helix that can associate with a second L domain to form a three-dimensional bilobal structure surrounding a central space of sufficient size to accommodate a ligand molecule.

As used herein, a furin domain is a domain recognized as such by those of skill in the art and is a cysteine rich region. Furin is a type 1 transmembrane serine protease. A furin domain functions as a cleavage site for furin protease

As used herein a Sema domain is a domain recognized as such by those of skill in the art and is a receptor recognition and binding module. The Sema domain is characterized by a conserved set of cysteine residues, which form four disulfide bonds to stabilize the structure. The Sema domain fold is a variation of a  $\beta$  propeller topology, with seven blades radially arranged around a central axis. Each blade contains a four-stranded antiparallel  $\beta$  sheet. The Sema domain uses a 'loop and hook' system to close the circle between the first and the last blades. The blades are constructed sequentially with an N-terminal  $\beta$ -strand closing the circle by providing the outermost strand of the seventh (C-terminal) blade. The  $\beta$ -propeller is further stabilized by an extension of the N-terminus, providing an additional, fifth  $\beta$ -strand on the outer edge of blade 6.

As used herein, a plexin domain is a domain recognized as such by those of skill in the art and contains a cysteine rich repeat. Plexins are receptors that as a complex interact with membrane-bound semaphorins. The plexins contain three domains with homology to c-met, the receptor for scatter factor-induced motility, but they lack the intrinsic tyrosine kinase activity of c-met. Intracellularly, invariant arginines identify a plexin domain with homology to guanosine triphosphatase-activating proteins. A protein can contain one, or more than one, plexin domain. As described herein, the MET receptor contains a single plexin domain.

As used herein, the F 5/8 type C domain is a domain recognized as such by those of skill in the art and is a domain that exhibits a distorted jelly-roll  $\beta$ -barrel motif, containing eight antiparallel strands arranged in two  $\beta$ -sheets. The lower part of the  $\beta$ -barrel is characterized by a preponderance of basic residues and three adjacent

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protruding loops. The portion of the polypeptide that forms the F 5/8 type C domain contains two conserved cysteines, which link the extremities of the domain by a disulfide bond.

As used herein an Ig-like domain is a domain recognized as such by those of skill in the art and is a domain containing folds of beta strands forming a compact folded structure of two beta sheets stabilized by hydrophobic interactions and sandwiched together by an intra-chain disulfide bond. In one example, an Ig-like C-type domain contains seven beta strands arranged as four-strand plus three-strand so that four beta strands form one beta sheet and three beta strands form the second beta sheet. In another example, an Ig-like V-type domain contains nine beta strands arranged as four beta strands plus five beta strands (Janeway C.A. et al. (eds): Immunobiology-the immune system in health and disease, 5th edn. New York, Garland Publishing, 2001.).

As used herein, a fibronectin type-III (FN3) domain is a domain recognized as such by those of skill in the art and contains a conserved  $\beta$  sandwich fold with one  $\beta$  sheet containing four strands and the other sheet containing three strands. The folded structure of an FN3 domain and an Ig-like domain are topologically very similar except the FN3 domain lacks a conserved disulfide bond. The portion of the polypeptide encoding an FN3 domain also is characterized by a short stretch of amino acids containing an Arg-Gly-Asp (RGD) that mediates interactions with cell adhesion molecules to modulate thrombosis, inflammation, and tumor metastasis. In one example, EphA1 contains two FN3 domains.

As used herein, an IPT/TIG domain is a domain recognized as such by those of skill in the art and has an immunoglobulin fold-like domain. Proteins contain one, or more than one, IPT/TIG domain. IPT/TIG domains are found in plexins, transcription factors, and extracellular regions of receptor proteins, such as for example the cell surface receptors MET and RON as described herein, that appear to regulate cell proliferation and cellular adhesion (Johnson CA et al, Journal of Medical Genetics, 40:311-319, (2003)).

As used herein, an EGF domain is a domain recognized as such by those of skill in the art and contains a repeat pattern involving a number of conserved cysteine

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residues which are important to the three-dimensional structure of the protein, and hence its recognition by receptors and other molecules. The EGF domain as described herein contains six cysteine residues which are involved in forming disulfide bonds. An EGF domain forms a two-stranded  $\beta$  sheet followed by a loop to a C-terminal short two-stranded sheet. Subdomains between the conserved cysteines vary in length. Repeats of EGF domains are typically found in the extracellular domain of membrane-bound proteins, such as for example in Tie-1 as described herein. A variation of the EGF domain is the laminin (Lam) EGF domain which, as described herein, has eight instead of six conserved cysteines and therefore is longer than the average EGF module and contains a further disulfide bond C-terminal of the EGF-like region.

As used herein, a C6 domain is a cysteine rich domain of typically about 110 to 160 amino acids in the N-terminal region of the polypeptide. It can be subdivided into four, or in some cases three or more, modules of about 40 residues containing 6 conserved cysteines that participate in intrachain disulfide bonds. A protein can have one, or more than one, C6 domain. As described herein, for example, TNFR2 contains three C6 domains.

As used herein, a transmembrane domain spans the plasma membrane anchoring the receptor and generally includes hydrophobic residues.

As used herein, a cytoplasmic domain is a domain that participates in signal transduction and occurs in the cytoplasmic portion of a transmembrane cell surface receptor. In one example, the cytoplasmic domain can include a protein kinase (PK) domain. A PK domain is recognized as such by those of skill in the art and is a domain that contains a conserved catalytic core. The conserved catalytic core is recognized to have a glycine-rich stretch of residues in the vicinity of a lysine residue in the N-terminal extremity of the domain, which has been shown to be involved in ATP binding, and an aspartic acid residue in the central part of the catalytic domain, which is important for the catalytic activity of the enzyme. Typically, the PK domain can be a serine/threonine protein kinase or a tyrosine protein kinase domain depending on the substrate specificity of the receptor domain such that, for example, a protein containing a tyrosine kinase domain phosphorylates substrate proteins on



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tyrosine residues whereas, for example, a protein containing a serine/threonine protein kinase domain phosphorylates substrate proteins on serine or threonine residues.

As used herein, sterile  $\alpha$  motif (SAM) domain is considered a protein-protein interaction module. A SAM domain is recognized as such by those of skill in the art and is a domain that spreads over typically about 70 residues to form an independently folded structure arranged in a small five-helix bundle with two large interfaces. In one example, such as for example in the SAM domain of EphB2, each of the interfaces is able to form dimers. The ability of the SAM domain to form homo- or hetero-oligomers creates a binding surface that mediates protein protein interactions.

As used herein, an allelic variant or allelic variation references to a polypeptide encoded by a gene that differs from a reference form of a gene (i.e. is encoded by an allele). Typically the reference form of the gene encodes a wildtype form and/or predominant form of a polypeptide from a population or single reference member of a species. Typically, allelic variants, which include variants between and among species typically have at least 80%, 90% or greater amino acid identity with a wildtype and/or predominant form from the same species; the degree of identity depends upon the gene and whether comparison is interspecies or intraspecies.. Generally, intraspecies allelic variants have at least about 80%, 85%, 90% or 95% identity or greater with a wildtype and/or predominant form, including 96%, 97%, 98%, 99% or greater identity with a wildtype and/or predominant form of a polypeptide.

As used herein, modification in reference to modification of a sequence of amino acids of a polypeptide or a sequence of nucleotides in a nucleic acid molecule and includes deletions, insertions, and replacements of amino acids and nucleotides, respectively.

As used herein, an open reading frame refers to a sequence of nucleotides that encodes a functional polypeptide or a portion thereof, typically at least about fifty amino acids. An open reading frame can encode a full-length polypeptide or a portion thereof. An open reading frame can be generated by operatively linking one or more

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exons or an exon and intron, when the stop codon is in the intron and all or a portion of the intron is in a transcribed mRNA.

As used herein, a polypeptide refers to two or more amino acids covalently joined. The terms "polypeptide" and "protein" are used interchangeably herein.

5 As used herein, truncation or shortening with reference to the shortening of a nucleic acid molecule or protein, refers to a sequence of nucleotides or amino acids that is less than full-length compared to a wildtype or predominant form of the protein or nucleic acid molecule.

As used herein, a reference gene refers to a gene that can be used to map  
10 introns and exons within a gene. A reference gene can be genomic DNA or portion thereof, that can be compared with, for example, an expressed gene sequence, to map introns and exons in the gene. A reference gene also can be a gene encoding a wildtype or predominant form of a polypeptide.

As used herein, a family or related family of proteins or genes refers to a  
15 group of proteins or genes, respectively that have homology and/or structural similarity and/or functional similarity with each other.

As used herein, a premature stop codon is a stop codon occurring in the open reading frame of a sequence before the stop codon used to produce or create a full-length form of a protein, such as a wildtype or predominant form of a polypeptide.  
20 The occurrence of a premature stop codon can be the result of, for example, alternative splicing and mutation.

As used herein, an expressed gene sequence refers to any sequence of nucleotides transcribed or predicted to be transcribed from a gene. Expressed gene sequences include, but are not limited to, cDNAs, ESTs, and *in silico* predictions of  
25 expressed sequences, for example, based on splice site predictions and *in silico* generation of spliced sequences.

As used herein, an expressed sequence tag (EST) is a sequence of nucleotides generated from an expressed gene sequence. ESTs are generated by using a population of mRNA to produce cDNA. The cDNA molecules can be produced for  
30 example, by priming from the polyA tail present on mRNAs. cDNA molecules also can be produced by random priming using one or more oligonucleotides which prime

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cDNA synthesis internally in mRNAs. The generated cDNA molecules are sequenced and the sequences are typically stored in a database. An example of an EST database is dbEST found online at [ncbi.nlm.nih.gov/dbEST](http://ncbi.nlm.nih.gov/dbEST). Each EST sequence is typically assigned a unique identifier and information such as the  
5 nucleotide sequence, length, tissue type where expressed, and other associated data is associated with the identifier.

As used herein, a kinase is a protein that is able to phosphorylate a molecule, typically a biomolecule, including macromolecules and small molecules. For example, the molecule can be a small molecule, or a protein. Phosphorylation  
10 includes auto-phosphorylation. Some kinases have constitutive kinase activity. Other kinases require activation. For example, many kinases that participate in signal transduction are phosphorylated. Phosphorylation activates their kinase activity on another biomolecule in a pathway. Some kinases are modulated by a change in protein structure and/or interaction with another molecule. For example,  
15 complexation of a protein or binding of a molecule to a kinase can activate or inhibit kinase activity.

As used herein, designated refers to the selection of a molecule or portion thereof as a point of reference or comparison. For example, a domain can be selected as a designated domain for the purpose of constructing polypeptides that are modified  
20 within the selected domain. In another example, an intron can be selected as a designated intron for the purpose of identifying RNA transcripts that include or exclude the selected intron.

As used herein, modulate and modulation refer to a change of an activity of a molecule, such as a protein. Exemplary activities include, but are not limited to,  
25 biological activities, such as signal transduction and protein phosphorylation. Modulation can include an increase in the activity (*i.e.*, up-regulation agonist activity) a decrease in activity (*i.e.*, down-regulation or inhibition) or any other alteration in an activity (such as periodicity, frequency, duration, kinetics). Modulation can be context dependent and typically modulation is compared to a designated state, for  
30 example, the wildtype protein, the protein in a constitutive state, or the protein as expressed in a designated cell type or condition.

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As used herein, inhibit and inhibition refer to a reduction in an activity, such as a biological activity, relative to the uninhibited activity.

As used herein, a composition refers to any mixture. It can be a solution, a suspension, liquid, powder, a paste, aqueous, non-aqueous or any combination  
5 thereof.

As used herein, a combination refers to any association between or among two or more items. The combination can be two or more separate items, such as two compositions or two collections, can be a mixture thereof, such as a single mixture of the two or more items, or any variation thereof. The elements of a combination are  
10 generally functionally associated or related. A kit is a packaged combination that optionally includes instructions for use of the combination or elements thereof and/or optionally include other reagents and vessels and tools and devices employed in the methods for which the kits are intended.

As used herein, a pharmaceutical effect refers to an effect observed upon  
15 administration of an agent intended for treatment of a disease or disorder or for amelioration of the symptoms thereof.

As used herein, treatment means any manner in which the symptoms of a condition, disorder or disease or other indication, are ameliorated or otherwise beneficially altered.

As used herein therapeutic effect means an effect resulting from treatment of a  
20 subject that alters, typically improves or ameliorates the symptoms of a disease or condition or that cures a disease or condition. A therapeutically effective amount refers to the amount of a composition, molecule or compound which results in a therapeutic effect following administration to a subject.

As used herein, the term "subject" refers to animals, including mammals, such  
25 as human beings. As used herein, a patient refers to a human subject.

As used herein, an activity refers to a function or functioning or changes in or interactions of a biomolecule, such as polypeptide. Exemplary, but not limiting of such activities are: complexation, dimerization, multimerization, receptor-associated  
30 kinase activity or other enzymatic or catalytic activity, receptor-associated protease activity, phosphorylation, dephosphorylation, autophosphorylation, ability to form

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complexes with other molecules, ligand binding, catalytic or enzymatic activity, activation including auto-activation and activation of other polypeptides, inhibition or modulation of another molecule's function, stimulation or inhibition of signal transduction and/or cellular responses such as cell proliferation, migration, differentiation, and growth, degradation, membrane localization, membrane binding, and oncogenesis. An activity can be assessed by assays described herein and by any suitable assays known to those of skill in the art, including, but not limited to *in vitro* assays, including cell-based assays, *in vivo* assays, including assays in animal models for particular diseases. Biological activities refer to activities exhibited *in vivo*. For purposes herein, biological activity refers to any of the activities exhibited by a polypeptide provided herein.

As used herein, angiogenic diseases (or angiogenesis-related diseases) are diseases in which the balance of angiogenesis is altered or the timing thereof is altered. Angiogenic diseases include those in which an alteration of angiogenesis, such as undesirable vascularization, occurs. Such diseases include, but are not limited to cell proliferative disorders, including cancers, diabetic retinopathies and other diabetic complications, inflammatory diseases, endometriosis and other diseases in which excessive vascularization is part of the disease process, including those noted above.

As used herein, complexation refers to the interaction of two or more molecules such as two molecules of a protein to form a complex. The interaction can be by noncovalent and/or covalent bonds and includes, but is not limited to, hydrophobic and electrostatic interactions, Van der Waals forces and hydrogen bonds. Generally, protein-protein interactions involve hydrophobic interactions and hydrogen bonds. Complexation can be influenced by environmental conditions such as temperature, pH, ionic strength and pressure, as well as protein concentrations.

As used herein, dimerization refers to the interaction of two molecules of the same type, such as two molecules of a receptor. Dimerization includes homodimerization where two identical molecules interact. Dimerization also includes heterodimerization of two different molecules, such as two subunits of a receptor and dimerization of two different receptor molecules. Typically, dimerization involves

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two molecules that interact with each other through interaction of a dimerization domain contained in each molecule.

As used herein, a ligand antagonist refers to the activity of a CSR isoform that antagonizes an activity that results from ligand interaction with a CSR.

5 As used herein, *in silico* refers to research and experiments performed using a computer. *In silico* methods include, but are not limited to, molecular modeling studies, biomolecular docking experiments, and virtual representations of molecular structures and/or processes, such as molecular interactions.

10 As used herein, biological sample refers to any sample obtained from a living or viral source or other source of macromolecules and biomolecules, and includes any cell type or tissue of a subject from which nucleic acid or protein or other macromolecule can be obtained. The biological sample can be a sample obtained directly from a biological source or to sample that is processed. For example, isolated nucleic acids that are amplified constitute a biological sample. Biological samples  
15 include, but are not limited to, body fluids, such as blood, plasma, serum, cerebrospinal fluid, synovial fluid, urine and sweat, tissue and organ samples from animals and plants and processed samples derived therefrom. Also included are soil and water samples and other environmental samples, viruses, bacteria, fungi algae, protozoa and components thereof.

20 As used herein, macromolecule refers to any molecule having a molecular weight from the hundreds up to the millions. Macromolecules include peptides, proteins, nucleotides, nucleic acids, and other such molecules that are generally synthesized by biological organisms, but can be prepared synthetically or using recombinant molecular biology methods.

25 As used herein, a biomolecule is any compound found in nature, or derivatives thereof. Exemplary biomolecules include but are not limited to: oligonucleotides, oligonucleosides, proteins, peptides, amino acids, peptide nucleic acids (PNAs), oligosaccharides and monosaccharides.

30 As used herein, the term "nucleic acid" refers to single-stranded and/or double-stranded polynucleotides such as deoxyribonucleic acid (DNA), and ribonucleic acid (RNA) as well as analogs or derivatives of either RNA or DNA.

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Also included in the term "nucleic acid" are analogs of nucleic acids such as peptide nucleic acid (PNA), phosphorothioate DNA, and other such analogs and derivatives or combinations thereof. Nucleic acid can refer to polynucleotides such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). The term also includes, as  
5 equivalents, derivatives, variants and analogs of either RNA or DNA made from nucleotide analogs, single (sense or antisense) and double-stranded polynucleotides. Deoxyribonucleotides include deoxyadenosine, deoxycytidine, deoxyguanosine and deoxythymidine. For RNA, the uracil base is uridine.

As used herein, the term "polynucleotide" refers to an oligomer or polymer  
10 containing at least two linked nucleotides or nucleotide derivatives, including a deoxyribonucleic acid (DNA), a ribonucleic acid (RNA), and a DNA or RNA derivative containing, for example, a nucleotide analog or a "backbone" bond other than a phosphodiester bond, for example, a phosphotriester bond, a phosphoramidate bond, a phosphorothioate bond, a thioester bond, or a peptide bond (peptide nucleic  
15 acid). The term "oligonucleotide" also is used herein essentially synonymously with "polynucleotide," although those in the art recognize that oligonucleotides, for example, PCR primers, generally are less than about fifty to one hundred nucleotides in length.

Polynucleotides can include nucleotide analogs, for example, mass  
20 modified nucleotides, which allow for mass differentiation of polynucleotides; nucleotides containing a detectable label such as a fluorescent, radioactive, luminescent or chemiluminescent label, which allow for detection of a polynucleotide; or nucleotides containing a reactive group such as biotin or a thiol group, which facilitates immobilization of a polynucleotide to a solid support. A  
25 polynucleotide also can contain one or more backbone bonds that are selectively cleavable, for example, chemically, enzymatically or photolytically. For example, a polynucleotide can include one or more deoxyribonucleotides, followed by one or more ribonucleotides, which can be followed by one or more deoxyribonucleotides, such a sequence being cleavable at the ribonucleotide sequence by base hydrolysis. A  
30 polynucleotide also can contain one or more bonds that are relatively resistant to cleavage, for example, a chimeric oligonucleotide primer, which can include

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nucleotides linked by peptide nucleic acid bonds and at least one nucleotide at the 3' end, which is linked by a phosphodiester bond or other suitable bond, and is capable of being extended by a polymerase. Peptide nucleic acid sequences can be prepared using well-known methods (see, for example, Weiler et al. Nucleic acids Res. 25: 2792-2799 (1997)).

As used herein, synthetic, in the context of a synthetic sequence and synthetic gene refers to a nucleic acid molecule that is produced by recombinant methods and/or by chemical synthesis methods.

As used herein, oligonucleotides refer to polymers that include DNA, RNA, nucleic acid analogues, such as PNA, and combinations thereof. For purposes herein, primers and probes are single-stranded oligonucleotides or are partially single-stranded oligonucleotides.

As used herein, primer refers to an oligonucleotide containing two or more deoxyribonucleotides or ribonucleotides, generally more than three, from which synthesis of a primer extension product can be initiated. Experimental conditions conducive to synthesis include the presence of nucleoside triphosphates and an agent for polymerization and extension, such as DNA polymerase, and a suitable buffer, temperature and pH.

As used herein, production by recombinant means by using recombinant DNA methods means the use of the well-known methods of molecular biology for expressing proteins encoded by cloned DNA.

As used herein, "isolated," with reference to a molecule, such as a nucleic acid molecule, oligonucleotide, polypeptide or antibody, indicates that the molecule has been altered by the hand of man from how it is found in its natural environment. For example, a molecule produced by and/or contained within a recombinant host cell is considered "isolated." Likewise, a molecule that has been purified, partially or substantially, from a native source or recombinant host cell, or produced by synthetic methods, is considered "isolated." Depending on the intended application, an isolated molecule can be present in any form, such as in an animal, cell or extract thereof; dehydrated, in vapor, solution or suspension; or immobilized on a solid support.



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As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is an episome, i.e., a nucleic acid capable of extra chromosomal replication. Vectors include those capable of autonomous replication and/or expression of nucleic acids to which they are linked. Vectors capable of directing the expression of genes to which they are operatively linked are referred to herein as "expression vectors." In general, expression vectors are often in the form of "plasmids," which are generally circular double stranded DNA loops that, in their vector form are not bound to the chromosome. "Plasmid" and "vector" are used interchangeably as the plasmid is the most commonly used form of vector. Other such other forms of expression vectors that serve equivalent functions and that become known in the art subsequently hereto.

As used herein, "transgenic animal" refers to any animal, generally a non-human animal, e.g., a mammal, bird or an amphibian, in which one or more of the cells of the animal contain heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. This molecule can be stably integrated within a chromosome, i.e., replicate as part of the chromosome, or it can be extrachromosomally replicating DNA. In the typical transgenic animals, the transgene causes cells to express a recombinant form of a protein.

As used herein, a reporter gene construct is a nucleic acid molecule that includes a nucleic acid encoding a reporter operatively linked to a transcriptional control sequences. Transcription of the reporter gene is controlled by these sequences. The activity of at least one or more of these control sequences is directly or indirectly regulated by another molecule such as a cell surface protein, a protein or small molecule involved in signal transduction within the cell. The transcriptional control sequences include the promoter and other regulatory regions, such as enhancer sequences, that modulate the activity of the promoter, or control sequences that modulate the activity or efficiency of the RNA polymerase. Such sequences are herein collectively referred to as transcriptional control elements or sequences. In addition,

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the construct can include sequences of nucleotides that alter translation of the resulting mRNA, thereby altering the amount of reporter gene product.

As used herein, "reporter" or "reporter moiety" refers to any moiety that allows for the detection of a molecule of interest, such as a protein expressed by a cell, or a biological particle. Typical reporter moieties include, for example, fluorescent proteins, such as red, blue and green fluorescent proteins (see, *e.g.*, U.S. Patent No. 6,232,107, which provides GFPs from *Renilla* species and other species), the lacZ gene from *E. coli*, alkaline phosphatase, chloramphenicol acetyl transferase (CAT) and other such well-known genes. For expression in cells, nucleic acid encoding the reporter moiety, referred to herein as a "reporter gene," can be expressed as a fusion protein with a protein of interest or under to the control of a promoter of interest.

As used herein, the phrase "operatively linked" with reference to sequences of nucleic acids means the nucleic acid molecules or segments thereof are covalently joined into one piece of nucleic acid such as DNA or RNA, whether in single or double stranded form. The segments are not necessarily contiguous, rather two or more components are juxtaposed so that the components are in a relationship permitting them to function in their intended manner. For example, segments of RNA (exons) can be operatively linked such as by splicing, to form a single RNA molecule. In another example, DNA segments can be operatively linked, whereby control or regulatory sequences on one segment control permit expression or replication or other such control of other segments. Thus, in the case of a regulatory region operatively linked to a reporter or any other polynucleotide, or a reporter or any polynucleotide operatively linked to a regulatory region, expression of the polynucleotide/reporter is influenced or controlled (*e.g.*, modulated or altered, such as increased or decreased) by the regulatory region. For gene expression, a sequence of nucleotides and a regulatory sequence(s) are connected in such a way to control or permit gene expression when the appropriate molecular signal, such as transcriptional activator proteins, are bound to the regulatory sequence(s). Operative linkage of heterologous nucleic acid, such as DNA, to regulatory and effector sequences of nucleotides, such as promoters, enhancers, transcriptional and translational stop sites, and other signal

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sequences, refers to the relationship between such DNA and such sequences of nucleotides. For example, operative linkage of heterologous DNA to a promoter refers to the physical relationship between the DNA and the promoter such that the transcription of such DNA is initiated from the promoter by an RNA polymerase that specifically recognizes, binds to and transcribes the DNA in reading frame.

As used herein, the term "operatively linked" with reference to amino acids in polypeptides refers to covalent linkage (direct or indirect) of the amino acids. For example, when used in the context of the phrase "at least one domain of a cell surface receptor operatively linked to at least one amino acid encoded by an intron of a gene encoding a cell surface receptor", means that the amino acids of a domain from a cell surface receptor are covalently joined to amino acids encoded by an intron from a cell surface receptor gene such as by linkage, typically direct linkage via peptide bonds, or the linkage also can be effected indirectly, such as via a linker or via non-peptidic linkage. Hence, a polypeptide that contains at least one domain of a cell surface receptor operatively linked to at least one amino acid encoded by an intron of a gene encoding a cell surface receptor can be an intron fusion protein. It contains one or more amino acids that are not found in a predominant form of the receptor but rather contains a portion that is encoded by an intron of the gene that encodes the predominant form. These one or more amino acids are encoded by an intron sequence of the gene encoding the cell surface receptor. Nucleic acids encoding such polypeptides can be produced when an intron sequence is spliced or otherwise covalently joined in-frame to an exon sequence that encodes a domain of a cell surface receptor. Translation of the nucleic acid molecule produces a polypeptide where the amino acid(s) of the intron sequence are covalently joined to a domain of the cell surface receptor. They also can be produced synthetically by linking a portion containing an exon to a portion containing an intron, including chimeric intron fusion proteins in which the exon is encoded by a gene for a different cell surface receptor isoform from the intron portion.

As used herein, the phrase "generated from a nucleic acid" in reference to the generating of a polypeptide, such as an isoform and intron fusion protein, includes the literal generation of a polypeptide molecule and the generation of an amino acid

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sequence of a polypeptide from translation of the nucleic acid sequence into a sequence of amino acids.

As used herein, a promoter region refers to the portion of DNA of a gene that controls transcription of the DNA to which it is operatively linked. The promoter region includes specific sequences of DNA that are sufficient for RNA polymerase recognition, binding and transcription initiation. This portion of the promoter region is referred to as the promoter. In addition, the promoter region includes sequences that modulate this recognition, binding and transcription initiation activity of the RNA polymerase. These sequences can be cis acting or can be responsive to trans acting factors. Promoters, depending upon the nature of the regulation, can be constitutive or regulated.

As used herein, regulatory region means a cis-acting nucleotide sequence that influences expression, positively or negatively, of an operatively linked gene. Regulatory regions include sequences of nucleotides that confer inducible (i.e., require a substance or stimulus for increased transcription) expression of a gene. When an inducer is present or at increased concentration, gene expression can be increased. Regulatory regions also include sequences that confer repression of gene expression (i.e., a substance or stimulus decreases transcription). When a repressor is present or at increased concentration gene expression can be decreased. Regulatory regions are known to influence, modulate or control many *in vivo* biological activities including cell proliferation, cell growth and death, cell differentiation and immune modulation. Regulatory regions typically bind to one or more trans-acting proteins, which results in either increased or decreased transcription of the gene.

Particular examples of gene regulatory regions are promoters and enhancers. Promoters are sequences located around the transcription or translation start site, typically positioned 5' of the translation start site. Promoters usually are located within 1 Kb of the translation start site, but can be located further away, for example, 2 Kb, 3 Kb, 4 Kb, 5 Kb or more, up to and including 10 Kb. Enhancers are known to influence gene expression when positioned 5' or 3' of the gene, or when positioned in or a part of an exon or an intron. Enhancers also can function at a significant distance

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from the gene, for example, at a distance from about 3 Kb, 5 Kb, 7 Kb, 10 Kb, 15 Kb or more.

Regulatory regions also include, in addition to promoter regions, sequences that facilitate translation, splicing signals for introns, maintenance of the correct  
5 reading frame of the gene to permit in-frame translation of mRNA, stop codons, leader sequences and fusion partner sequences, internal ribosome binding sites (IRES), elements for the creation of multigene or polycistronic messages, polyadenylation signals to provide proper polyadenylation of the transcript of a gene of interest and stop codons and can be optionally included in an expression vector.

10 As used herein, the "amino acids," which occur in the various amino acid sequences appearing herein, are identified according to their well-known, three-letter or one-letter abbreviations (see Table 1). The nucleotides, which occur in the various DNA fragments, are designated with the standard single-letter designations used routinely in the art.

15 As used herein, "amino acid residue" refers to an amino acid formed upon chemical digestion (hydrolysis) of a polypeptide at its peptide linkages. The amino acid residues described herein are generally in the "L" isomeric form. Residues in the "D" isomeric form can be substituted for any L-amino acid residue, as long as the desired functional property is retained by the polypeptide. NH<sub>2</sub> refers to the free  
20 amino group present at the amino terminus of a polypeptide. COOH refers to the free carboxy group present at the carboxyl terminus of a polypeptide. In keeping with standard polypeptide nomenclature described in J. Biol. Chem., 243:3552-59 (1969) and adopted at 37 C.F.R. §§ 1.821 - 1.822, abbreviations for amino acid residues are shown in Table 1:

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**Table 1 – Table of Correspondence**

<b>SYMBOL</b>		
<b>1-Letter</b>	<b>3-Letter</b>	<b>AMINO ACID</b>
Y	Tyr	tyrosine
G	Gly	glycine
F	Phe	phenylalanine
M	Met	methionine
A	Ala	alanine
S	Ser	serine
I	Ile	isoleucine
L	Leu	leucine
T	Thr	threonine
V	Val	valine
P	Pro	proline
K	Lys	lysine
H	His	Histidine
Q	Gln	Glutamine
E	Glu	glutamic acid
Z	Glx	Glu and/or Gln
W	Trp	Tryptophan
R	Arg	Arginine
D	Asp	aspartic acid
N	Asn	Asparagines
B	Asx	Asn and/or Asp
C	Cys	Cysteine
X	Xaa	Unknown or other

All sequences of amino acid residues represented herein by a formula have a left to right orientation in the conventional direction of amino-terminus to carboxyl-terminus. In addition, the phrase “amino acid residue” is defined to include the amino acids listed in the Table of Correspondence modified, non-natural and unusual amino acids. Furthermore, it should be noted that a dash at the beginning or end of an amino acid residue sequence indicates a peptide bond to a further sequence of one or more amino acid residues or to an amino-terminal group such as  $\text{NH}_2$  or to a carboxyl-terminal group such as  $\text{COOH}$ .

In a peptide or protein, suitable conservative substitutions of amino acids are known to those of skill in this art and generally can be made without altering a biological activity of a resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do

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not substantially alter biological activity (see, *e.g.*, Watson *et al. Molecular Biology of the Gene*, 4th Edition, 1987, The Benjamin/Cummings Pub. co., p.224).

Such substitutions may be made in accordance with those set forth in TABLE 2 as follows:

5

**TABLE 2**

<b>Original residue</b>	<b>Conservative substitution</b>
Ala (A)	Gly; Ser
Arg (R)	Lys
Asn (N)	Gln; His
Cys (C)	Ser
Gln (Q)	Asn
Glu (E)	Asp
Gly (G)	Ala; Pro
His (H)	Asn; Gln
Ile (I)	Leu; Val
Leu (L)	Ile; Val
Lys (K)	Arg; Gln; Glu
Met (M)	Leu; Tyr; Ile
Phe (F)	Met; Leu; Tyr
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr
Tyr (Y)	Trp; Phe
Val (V)	Ile; Leu

Other substitutions also are permissible and can be determined empirically or in accord with other known conservative or non-conservative substitutions.

As used herein, a peptidomimetic is a compound that mimics the conformation and certain stereochemical features of a biologically active form of a particular peptide. In general, peptidomimetics are designed to mimic certain desirable properties of a compound, but not the undesirable properties, such as flexibility, that lead to a loss of a biologically active conformation and bond breakdown. Peptidomimetics can be prepared from biologically active compounds by replacing certain groups or bonds that contribute to the undesirable properties with bioisosteres. Bioisosteres are known to those of skill in the art. For example the methylene bioisostere CH<sub>2</sub>S has been used as an amide replacement in enkephalin analogs (see, *e.g.*, Spatola (1983) pp. 267-357 in *Chemistry and Biochemistry of Amino Acids*,

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Peptides, and Proteins, Weinstein, Ed. volume 7, Marcel Dekker, New York).

Morphine, which can be administered orally, is a compound that is a peptidomimetic of the peptide endorphin. For purposes herein, polypeptides in which one or more peptidic bonds that form the backbone of a polypeptide are replaced with bioisoteres  
5 are peptidomimetics.

As used herein, "similarity" between two proteins or nucleic acids refers to the relatedness between the amino acid sequences of the proteins or the nucleotide sequences of the nucleic acids. Similarity can be based on the degree of identity and/or homology of sequences of residues and the residues contained therein.

10 Methods for assessing the degree of similarity between proteins or nucleic acids are known to those of skill in the art. For example, in one method of assessing sequence similarity, two amino acid or nucleotide sequences are aligned in a manner that yields a maximal level of identity between the sequences. "Identity" refers to the extent to which the amino acid or nucleotide sequences are invariant. Alignment of amino acid  
15 sequences, and to some extent nucleotide sequences, also can take into account conservative differences and/or frequent substitutions in amino acids (or nucleotides). Conservative differences are those that preserve the physico-chemical properties of the residues involved. Alignments can be global (alignment of the compared sequences over the entire length of the sequences and including all residues) or local  
20 (the alignment of a portion of the sequences that includes only the most similar region or regions).

"Identity" per se has an art-recognized meaning and can be calculated using published techniques. (See, e.g.: *Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome  
25 Projects*, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data*, Part I, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987; and *Sequence Analysis Primer*, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991). While there exist a number of methods to measure  
30 identity between two polynucleotide or polypeptides, the term "identity" is well



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known to skilled artisans (Carillo, H. & Lipton, D., *SIAM J Applied Math* 48:1073 (1988)).

As used herein, sequence identity compared along the full length of a polypeptide compared to another polypeptide refers to the percentage of identity of an amino acid in a polypeptide along its full-length. For example, if a polypeptide A has 100 amino acids and polypeptide B has 95 amino acids, identical to amino acids 1-95 of polypeptide A, then polypeptide B has 95% identity when sequence identity is compared along the full length of a polypeptide A compared to full length of polypeptide B. As discussed below, and known to those of skill in the art, various programs and methods for assessing identity are known to those of skill in the art. High levels of identity, such as 90% or 95% identity, readily can be determined without software.

As used herein, by homologous (with respect to nucleic acid and/or amino acid sequences) means about greater than or equal to 25% sequence homology, typically greater than or equal to 25%, 40%, 60%, 70%, 80%, 85%, 90% or 95% sequence homology; the precise percentage can be specified if necessary. For purposes herein the terms "homology" and "identity" are often used interchangeably, unless otherwise indicated. In general, for determination of the percentage homology or identity, sequences are aligned so that the highest order match is obtained (see, e.g.: *Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome Projects*, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data, Part I*, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987; and *Sequence Analysis Primer*, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; Carillo *et al.* (1988) *SIAM J Applied Math* 48:1073). By sequence homology, the number of conserved amino acids is determined by standard alignment algorithms programs, and can be used with default gap penalties established by each supplier. Substantially homologous nucleic acid molecules would hybridize typically at moderate stringency or at high stringency all along the length of the nucleic acid of

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interest. Also contemplated are nucleic acid molecules that contain degenerate codons in place of codons in the hybridizing nucleic acid molecule.

Whether any two nucleic acid molecules have nucleotide sequences that are at least 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% "identical" or  
5 "homologous" can be determined using known computer algorithms such as the "FAST A" program, using for example, the default parameters as in Pearson *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:2444 (other programs include the GCG program package (Devereux, J., *et al.*, *Nucleic Acids Research* 12(I):387 (1984)), BLASTP, BLASTN, FASTA (Atschul, S.F., *et al.*, *J Molec Biol* 215:403 (1990); Guide to Huge  
10 Computers, Martin J. Bishop, ed., Academic Press, San Diego, 1994, and Carillo *et al.* (1988) *SIAM J Applied Math* 48:1073). For example, the BLAST function of the National Center for Biotechnology Information database can be used to determine identity. Other commercially or publicly available programs include, DNASTar "MegAlign" program (Madison, WI) and the University of Wisconsin Genetics  
15 Computer Group (UWG) "Gap" program (Madison WI)). Percent homology or identity of proteins and/or nucleic acid molecules can be determined, for example, by comparing sequence information using a GAP computer program (*e.g.*, Needleman *et al.* (1970) *J. Mol. Biol.* 48:443, as revised by Smith and Waterman ((1981) *Adv. Appl. Math.* 2:482). Briefly, the GAP program defines similarity as the number of aligned  
20 symbols (*i.e.*, nucleotides or amino acids), which are similar, divided by the total number of symbols in the shorter of the two sequences. Default parameters for the GAP program can include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) and the weighted comparison matrix of Gribskov *et al.* (1986) *Nucl. Acids Res.* 14:6745, as described by Schwartz and Dayhoff, eds.,  
25 *ATLAS OF PROTEIN SEQUENCE AND STRUCTURE*, National Biomedical Research Foundation, pp. 353-358 (1979); (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps.

Therefore, as used herein, the term "identity" or "homology" represents a comparison between a test and a reference polypeptide or polynucleotide. As used  
30 herein, the term at least "90% identical to" refers to percent identities from 90 to 99.99 relative to the reference nucleic acid or amino acid sequences. Identity at a level of

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90% or more is indicative of the fact that, assuming for exemplification purposes a test and reference polypeptide length of 100 amino acids are compared, no more than 10% (*i.e.*, 10 out of 100) of the amino acids in the test polypeptide differs from that of the reference polypeptide. Similar comparisons can be made between test and  
5 reference polynucleotides. Such differences can be represented as point mutations randomly distributed over the entire length of an amino acid sequence or they can be clustered in one or more locations of varying length up to the maximum allowable, *e.g.* 10/100 amino acid difference (approximately 90% identity). Differences are defined as nucleic acid or amino acid substitutions, insertions or deletions. At the  
10 level of homologies or identities above about 85-90%, the result should be independent of the program and gap parameters set; such high levels of identity can be assessed readily, often by manual alignment without relying on software.

As used herein, an aligned sequence refers to the use of homology (similarity and/or identity) to align corresponding positions in a sequence of nucleotides or  
15 amino acids. Typically, two or more sequences that are related by 50% or more identity are aligned. An aligned set of sequences refers to 2 or more sequences that are aligned at corresponding positions and can include aligning sequences derived from RNAs, such as ESTs and other cDNAs, aligned with genomic DNA sequence.

As used herein, "primer" refers to a nucleic acid molecule that can act as a  
20 point of initiation of template-directed DNA synthesis under appropriate conditions (*e.g.*, in the presence of four different nucleoside triphosphates and a polymerization agent, such as DNA polymerase, RNA polymerase or reverse transcriptase) in an appropriate buffer and at a suitable temperature. It will be appreciated that certain nucleic acid molecules can serve as a "probe" and as a "primer." A primer, however,  
25 has a 3' hydroxyl group for extension. A primer can be used in a variety of methods, including, for example, polymerase chain reaction (PCR), reverse-transcriptase (RT)-PCR, RNA PCR, LCR, multiplex PCR, panhandle PCR, capture PCR, expression PCR, 3' and 5' RACE, *in situ* PCR, ligation-mediated PCR and other amplification protocols.

30 As used herein, "primer pair" refers to a set of primers that includes a 5' (upstream) primer that hybridizes with the 5' end of a sequence to be amplified (*e.g.*

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by PCR) and a 3' (downstream) primer that hybridizes with the complement of the 3' end of the sequence to be amplified.

As used herein, "specifically hybridizes" refers to annealing, by complementary base-pairing, of a nucleic acid molecule (*e.g.* an oligonucleotide) to a target nucleic acid molecule. Those of skill in the art are familiar with *in vitro* and *in vivo* parameters that affect specific hybridization, such as length and composition of the particular molecule. Parameters particularly relevant to *in vitro* hybridization further include annealing and washing temperature, buffer composition and salt concentration. Exemplary washing conditions for removing non-specifically bound nucleic acid molecules at high stringency are 0.1 x SSPE, 0.1% SDS, 65°C, and at medium stringency are 0.2 x SSPE, 0.1% SDS, 50°C. Equivalent stringency conditions are known in the art. The skilled person can readily adjust these parameters to achieve specific hybridization of a nucleic acid molecule to a target nucleic acid molecule appropriate for a particular application.

As used herein, an effective amount is the quantity of a therapeutic agent necessary for preventing, curing, ameliorating, arresting or partially arresting a symptom of a disease or disorder.

As used herein, unit dose form refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art.

## **B. Cell Surface Receptor (CSR) Isoforms**

Provided herein are cell surface receptor (CSR) isoforms, families of CSR isoforms and methods of preparing CSR isoforms. The CSR isoforms differ from the cognate receptors in that there are insertions and/or deletions and the resulting CSR isoforms exhibit a difference in one or more activities or functions compared to the cognate receptor. Such changes include a change in a biological activity, such as elimination of kinase activity, and/or elimination of all or part of a transmembrane domain. The CSR isoforms provided herein can be used for modulating the activity of a cell surface receptor. They also can be used as targeting agents for delivery of molecules, such as drugs or toxins or nucleic acids, to targeted cells or tissues.

CSR isoforms can contain a new domain and/or exhibit a new or different biological function compared to a wildtype and/or predominant form of the receptor.

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For example, intron-encoded amino acids can introduce a new domain or portion thereof into an isoform. Biological activities that can be altered include, but are not limited to, protein-protein interactions such as dimerization, multimerization and complex formation, specificity and/or affinity for ligand, cellular localization and  
5 relocalization, membrane anchoring, enzymatic activity such as kinase activity, response to regulatory molecules including regulatory proteins, cofactors, and other signaling molecules, such as in a signal transduction pathway. Generally, a biological activity is altered in an isoform at least 0.1, 0.5, 1, 2, 3, 4, 5, or 10 fold compared to a wildtype and/or predominant form of the receptor. Typically, a  
10 biological activity is altered 10, 20, 50, 100 or 1000 fold or more. For example, an isoform can be reduced in a biological activity.

CSR isoforms also can modulate an activity of a wildtype and/or predominant form of the receptor. For example, a CSR isoform can interact directly or indirectly with a CSR isoform and modulate a biological activity of the receptor. Biological  
15 activities that can be altered include, but are not limited to, protein-protein interactions such as dimerization, multimerization and complex formation, specificity and/or affinity for ligand, cellular localization and relocalization, membrane anchoring, enzymatic activity such as kinase activity, response to regulatory molecules including regulatory proteins, cofactors, and other signaling molecules,  
20 such as in a signal transduction pathway.

A CSR isoform can interact directly or indirectly with a cell surface receptor to cause or participate in a biological effect, such as by modulating a biological activity of the cell surface receptor. A CSR isoform also can interact independently of a cell surface receptor to cause a biological effect, such as by initiating or inhibiting  
25 a signal transduction pathway. For example, a CSR isoform can initiate a signal transduction pathway and enhance or promote cell growth. In another example, a CSR isoform can interact with the cell surface receptor as a ligand causing a biological effect for example by inhibiting a signal transduction pathway that can impede or inhibit cell growth. Hence, the isoforms provided herein can function as  
30 cell surface receptor ligands in that they interact with the targeted receptor in the same manner that a cognate ligand interacts with and alters receptor activity. The isoforms

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can bind as a ligand, but not necessarily, to a ligand binding site and serve to block receptor dimerization. They act as ligands in that they interact with the receptor. The CSR isoforms also can act by binding to ligands for the receptor and/or by preventing receptor activities, such as dimerization.

5           For example, a CSR isoform can compete with a CSR for ligand binding. A CSR isoform, when it binds to receptor, can be a negative effector ligand, which results in inhibition of receptor function. It also is possible that some CSR isoforms bind a cognate receptor, resulting in activation of the receptor. A CSR isoform can act as a competitive inhibitor of a CSR, for example, by complexing with a CSR  
10 isoform and altering the ability of the CSR to multimerize (*e.g.* dimerize or trimerize) with other CSRs. A CSR isoform can compete with a CSR for interactions with other polypeptides and cofactors in a signal transduction pathway. The cell surface isoforms and families of isoforms provided herein include, but are not limited to, isoforms of receptor tyrosine kinases (also referred to herein as RTK isoforms) and  
15 isoforms of other families of CSRs, such as TNFs and other G-protein-coupled receptors. In one example, a CSR isoform is a soluble polypeptide. For example, a CSR isoform lacks at least part or all of a transmembrane domain. Soluble isoforms can modulate a biological activity of a wildtype or predominant form of a receptor (see for example, Kendall *et al.* (1993) PNAS 90: 10705, Werner *et al.* (1992) Molec.  
20 Cell Biol. 12: 82, Heaney *et al.* (1995) PNAS 92: 2365, Fukunaga *et al.* (1990) PNAS 87:8702, Wypych *et al.* (1995) Blood 85: 66-73, Barron *et al.* (1994) Gene 147:263, Cheng *et al.* (1994) Science 263: 1759, Dastot *et al.* (1996) PNAS 93:10723, Abramovich *et al.* (1994) FEBS Lett 338:295, Diamant *et al.* (1997) FEBS Lett 412:379, Ku *et al.* (1996) Blood 88:4124, Heaney ML and Golde DW (1998), J  
25 Leukocyte Biol. 64:135-146).

A cell surface receptor isoform can be produced by any method known in the art including isolation of isoforms expressed in cells, tissues and organisms, and by recombinant methods and by methods including *in silico* steps, synthetic methods and any methods known to those of skill in the art. Isoforms of cell surface receptors,  
30 including isoforms of receptor tyrosine kinases, can be encoded by alternatively spliced RNA molecules transcribed from a receptor tyrosine kinase gene. Such

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isoforms include exon deletion, exon extension, exon truncation and intron retention alternatively spliced RNAs. CSR isoforms, include receptor isoforms that contain sequences encoded by introns (or alternative exons); also referred to as intron fusion proteins.

5           Pharmaceutical compositions containing one or more different CSR isoforms are provided. Also provided are methods of treatment of diseases and conditions by administering the pharmaceutical compositions or delivering a CSR isoform, such by administering a vector that encodes the isoform. Administration can be effected *in vivo* or *ex vivo*.

10           Methods of identifying and producing CSR isoforms and nucleic acid molecules encoding CSR isoforms are provided herein. Also provided are methods for expressing, isolating and formulating CSR isoforms.

#### **Classes of CSR Isoforms**

As noted, CSR isoforms are polypeptides that lack a domain or portion of a domain sufficient to remove or reduce or otherwise alter, including having a positive or negative effect, on biological activity compared to the cognate unbound form of the receptor. Some CSR isoforms also have completely novel functions as a result of the gain or loss of domains, or even single amino acid replacements. CSR isoforms represent splice variants of a gene (or recombinant shortened variants) and can be generated by alternate splicing or by recombinant or synthetic methods. CSR isoforms can be encoded by alternatively spliced RNAs. CSR isoforms also can be generated by recombinant methods and by use of *in silico* and synthetic methods.

Typically, a CSR isoform produced from an alternatively spliced RNA is not a predominant form of a polypeptide encoded by a gene. In some instances, a CSR isoform can be a tissue-specific or developmental stage-specific polypeptide or disease specific (*i.e.*, can be expressed at a difference level from tissue-to-tissue or stage-to-stage or in a disease state compared to a non-diseased state or only may be expressed in the tissue, at the stage or during the disease process or progress). Alternatively spliced RNA forms that can encode CSR isoforms include, but are not limited to, exon deletion, exon retention, exon extension, exon truncation, and intron

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retention alternatively spliced RNAs. Included among CSR isoforms are intron fusion proteins.

**(a) Alternative Splicing and Generation of CSR Isoforms**

Genes in eukaryotes include introns and exons that are transcribed by RNA  
5 polymerase into RNA products generally referred to as pre-mRNA. Pre-mRNAs are typically intermediate products that are further processed through RNA splicing and processing to generate a final messenger RNA (mRNA). Typically, a final mRNA contains exons sequences and is obtained by splicing out the introns. Boundaries of introns and exons are marked by splice junctions, sequences of nucleotides that are  
10 used by the splicing machinery of the cell as signals and substrates for removing introns and joining together exon sequences. Exons are operatively linked together to form a mature RNA molecule. Typically, one or more exons in an mRNA contains an open reading frame encoding a polypeptide. In many cases, an open reading frame can be generated by operatively linking two or more exons; for example, a coding  
15 sequence can span exon junctions and an open reading frame is maintained across the junctions.

RNA also can undergo alternative splicing to produce a variety of different mRNA transcripts from a single gene. Alternatively spliced mRNAs can contain different numbers of and/or arrangements of exons. For example, a gene that has 10  
20 exons can generate a variety of alternatively spliced mRNAs. Some mRNAs can contain all 10 exons, some with only 9, 8, 7, 6, 5 etc. In addition, products, for example, with 9 of the 10 exons, can be among a variety of mRNAs, each with a different exon missing. Alternatively spliced mRNAs can contain additional exons, not typically present in an RNA encoding a predominant or wild type form. Addition  
25 and deletion of exons includes addition and deletion, respectively of a 5' exon, 3' exon and an exon internal in an RNA. Alternatively spliced RNA molecules also include addition of an intron or a portion of an intron operatively linked to or within an RNA. For example, an intron normally removed by splicing in an RNA encoding a wildtype or predominant form can be present in an alternatively spliced RNA. An intron or  
30 intron portion can be operatively linked within an RNA, such as between two exons. An intron or intron portion can be operatively linked at one end of an RNA, such as at



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the 3' end of a transcript. In some examples, the presence of intron sequence within an RNA terminates transcription based on poly-adenylation sequences within an intron.

Alternative RNA splicing patterns can vary depending upon the cell and tissue type. Alternative RNA splicing also can be regulated by developmental stage of an organism, cell or tissue type. For example, RNA splicing enzymes and polypeptides that regulate RNA splicing can be present at different concentrations in particular cell and tissue types and at particular stages of development. In some cases, a particular enzyme or regulatory polypeptide can be absent from a particular cell or tissue type or at particular stage of development. These differences can produce different splicing patterns for an RNA within a cell or tissue type or stage, thus giving rise to different populations of mRNAs. Such complexity can generate a number of protein products appropriate for particular cell types or developmental stages.

Alternatively spliced mRNAs can generate a variety of different polypeptides, also referred to herein as isoforms. Such isoforms can include polypeptides with deletions, additions and shortenings. For example, a portion of an open reading frame normally encoded by an exon can be removed in an alternatively spliced mRNA, thus resulting in a shorter polypeptide. An isoform can have amino acids removed at the N or C terminus or the deletion can be internal. An isoform can be missing a domain or a portion of a domain as a result of a deleted exon. Alternatively spliced mRNAs also can generate polypeptides with additional sequences. For example, a stop codon can be contained in an exon; when this exon is not included in an mRNA, the stop codon is not present and the open reading frame continues into the sequences contained in downstream exons. In such examples, additional open reading frame sequences add additional amino acid sequences to a polypeptide and can include addition of a new domain or a portion thereof.

#### **(b) Intron Fusion Proteins**

One class of isoforms is intron fusion proteins. An intron fusion protein is an isoform that lacks a domain or portion of a domain sufficient to remove or reduce a biological activity of a receptor. In addition, an intron fusion protein contains one or more amino acids not encoded by an exon, operatively linked to exon-encoded amino

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acids and/or is shortened compared to a wildtype or predominant form encoded by a CSR gene. Typically, an intron fusion protein is shortened by the presence of one or more stop codons in an intron fusion protein-encoding RNA that are not present in the corresponding sequence of an RNA encoding a wildtype or predominant form of a CSR polypeptide. Addition of amino acids and/or a stop codon can result in an intron fusion protein that differs in size and sequence from a wildtype or predominant form of a polypeptide.

An intron fusion protein is modified in one or more biological activities. For example, addition of amino acids in an intron fusion protein can add, extend or modify a biological activity compared to a wildtype or predominant form of a polypeptide. For example, fusion of an intron encoded amino acid sequence to a protein can result in the addition of a domain with new functionality. Fusion of an intron encoded amino acid sequence to a protein also can modulate an existing biological activity of a protein, such as by inhibiting a biological activity, for example, inhibition of dimerization or inhibition of kinase activity.

Intron fusion proteins include natural and combinatorial intron fusion proteins. A natural intron fusion protein is encoded by an alternatively spliced RNA that contains one or more introns or a portion thereof operatively linked to one or more exons of a gene. A natural intron fusion protein contains one or more amino acids encoded by an intron sequence and/or an intron fusion protein can be shortened as a result of one or more stop codons encoded by an intron sequence operatively linked to one or more exons. A combinatorial intron fusion protein is a polypeptide that is shortened compared to a wildtype or predominant form of a polypeptide. Typically, the shortening removes one or more domains or a portion thereof from a polypeptide. Combinatorial intron fusion proteins often mimic a natural intron fusion protein in that one or more domains or a portion thereof is/are deleted as in a natural intron fusion protein derived from the same gene sequence or derived from a gene sequence in a related gene family.

**i. Natural intron fusion proteins**

Natural intron fusion proteins are generated from a class of alternatively spliced mRNAs that includes mRNAs that have incorporated intron sequences into

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mRNA as well as exon sequences, such as intron retention RNA molecules and some exon extension RNAs. They include all such variants that occur and can be isolated from a cell or tissue, identified in a database or synthesized based upon the sequence and structure of a gene. Any splice variant that is possible and that includes one or more codons (including only a stop codon) from an intron is considered a natural intron fusion protein.

The incorporated intron sequences can include one or more introns or a portion thereof. Such mRNAs can arise by a mechanism of intron retention. For example, a pre-mRNA is exported from the nucleus to the cytoplasm of the cell before the splicing machinery has removed one or more introns. In some cases, splice sites can be actively blocked, for example by cellular proteins, preventing splicing of one or more introns.

Retention of one or more introns or a portion thereof also can lead to the generation of isoforms referred to herein as natural intron fusion proteins. For example, an intron sequence can contain an open reading frame that is operatively linked to the exon sequences by RNA splicing. Intron-encoded sequences can add amino acids to a polypeptide, for example, at either the N or C terminus of a polypeptide, or internally within a polypeptide. In some examples, an intron sequence also can contain one or more stop codons. An intron encoded stop codon that is operatively linked with an open reading frame in one or more exons can terminate the encoded polypeptide. Thus, an isoform can be produced that is shortened as a result of the stop codon. In some examples, an intron retained in an mRNA can result in the addition of one or more amino acids and a stop codon to an open reading frame, thereby producing an isoform that terminates with an intron encoded sequence.

Provided herein are natural intron fusion proteins, that can be generated by intron retention, including intron fusion proteins with addition of domains or portion of domains encoded by an intron and intron fusion proteins with one or more domains or portion of domain deleted. For example, an intron sequence can be operatively linked in place of an exon sequence that is typically within an mRNA for a gene. A domain or portion thereof encoded by the exon is thus deleted from and intron encoded amino acids are included in the encoded polypeptide.

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In another example, an intron sequence is operatively linked in addition to the typically present exons in an mRNA. In one example, an operatively linked intron sequence can introduce a stop codon in-frame with exon sequences encoding a polypeptide. In another example, an operatively linked intron sequence can introduce one or more amino acids into a polypeptide. In some embodiments, a stop codon in-frame also is operatively linked with exon sequences encoding a polypeptide, thereby generating an mRNA encoding a polypeptide with intron-encoded amino acids at the C terminus.

In one example of a natural intron fusion protein, one or more amino acids encoded by an intron sequence are operatively linked at the C terminus of a polypeptide. For example, an intron fusion protein is generated from a nucleic acid sequence that contains one or more exon sequences at the 5' end of an RNA followed by one or more intron sequences or a portion of an intron sequence retained at the 3' end of an RNA. An intron fusion protein produced from such nucleic acid contains exon-encoded amino acids at the N-terminus and one or more amino acids encoded by an intron sequence at the C-terminus. In another example, an intron fusion protein is generated from a nucleic acid by operatively linking a stop codon encoded within an intron sequence to one or more exon sequences, thereby generating a nucleic acid sequence encoding shortened polypeptide.

## **ii. Combinatorial Intron fusion proteins**

Intron fusion proteins also can be generated by recombinant methods and/or *in silico* and synthetic methods to produce polypeptides that are modified compared to a wildtype or predominant form of a polypeptide. Typically, combinatorial intron fusion proteins are shortened polypeptides compared to a wildtype or predominant form. Shortening can remove one or more domains or a portion thereof.

Combinatorial intron fusion proteins are mimics of so-called natural intron fusion proteins in that one or more domains or a portion thereof that are deleted in a natural intron fusion protein derived from the same gene sequence or derived from a gene sequence in a related gene family is/are deleted. For example, as is described further herein, by aligning sequences of gene family members, intron and exons, structures and encoded protein domains can be identified in the nucleic acid.

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Recombinant nucleic acid molecules encoding polypeptides can be synthesized that contain one or more exons and an intron or portion thereof. Such recombinant molecules can contain one or more amino acids and/or a stop codon encoded by an intron, operatively linked to an exon, producing an intron fusion protein.

- 5    Recombinant polypeptides also can be produced that contain a combinatorial intron fusion protein. As part of this method, potential immunogenic epitopes can be recognized using motif scanning, and modified with conservative amino acid substitutions or by other modifications well known in the art, such as PEGylation. Generally, any therapeutic intron fusion protein can be modified in this same way to  
10    achieve optimized pharmacokinetics or avoid immunogenicity.

**(c)     Intron-encoded isoforms**

- Another CSR isoform is an intron-encoded isoform. An intron-encoded isoform contains an intron sequences or portions thereof from an isoform, such as a natural intron fusion protein. An intron-encoded isoform can interact with a wildtype  
15    form or predominant form of a polypeptide produced from the same gene as the intron-encoded isoform. An intron-encoded isoforms can interact with a molecule in a signal transduction pathway that interact with a wildtype form or predominant form of a polypeptide produced from the same gene as the intron-encoded isoform. An intron-encoded isoform can be expressed or produced as a fusion with exon-encoded  
20    sequences. An intron-encoded isoform can be expressed or produced as a fusion with heterologous sequences such as a starting methionine. Stop codons can be engineered in the encoding nucleic acid molecule to terminate an intron-encoded isoform within or at the end of the intron sequence.

**(d)     Isoforms generated by exon modifications**

- 25       CSR isoforms can be generated by modification of an exon relative to a corresponding exon of an RNA encoding a wildtype or predominant form of a CSR polypeptide. Exon modifications include alternatively spliced RNA forms such as exon truncations, exon extensions, exon deletions and exon insertions. These alternatively spliced RNA molecules can encode CSR isoforms which differ from a  
30    wildtype or predominant form of a CSR polypeptide by including additional amino

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acids and/or by lacking amino acid sequences present in a wildtype or predominant form of a CSR polypeptide.

Exon insertions are alternative spliced RNA molecules that contains at least one exon not typically present in an RNA encoding a wildtype or predominant form of a polypeptide. An inserted exon can operatively link additional amino acids encoded by the inserted exon to the other exons present in an RNA. An inserted exon also can contain one or more stop codons such that the RNA encoded polypeptide terminates as a result of such stop codons. If an exon containing such stop codons is inserted upstream of an exon that contains the stop codon used for polypeptide termination of a wildtype or predominant form of a polypeptide, a shortened polypeptide can be produced.

An inserted exon can maintain an open reading frame, such that when the exon is inserted, the RNA encodes an isoform containing an amino acid sequence of a wildtype or predominant form of a polypeptide with additional amino acids encoded by the inserted exon. An inserted exon can be inserted 5', 3' or internally in an RNA, such that additional amino acids encoded by the inserted exon are linked at the N terminus, C-terminus or internally, respectively in an isoform. An inserted exon also can change the reading frame of an RNA in which it is inserted, such that an isoform is produced that contains only a portion of the sequence of amino acids in a wildtype or predominant form of a polypeptide. Such isoforms can additionally contain amino acid sequence encoded by the inserted exon and also can terminate as a result of a stop codon contained in the inserted exon.

CSR isoforms also can be produced from exon deletion events. An exon deletion refers to an event of alternative RNA splicing that produces a nucleic acid molecule that lacks at least one exon compared to an RNA encoding a wildtype or predominant form of a polypeptide. Deletion of an exon can produce a polypeptide of alternate size such as by removing sequences that encode amino acids as well as by changing the reading frame of an RNA encoding a polypeptide. An exon deletion can remove one or more amino acids from an encoded polypeptide; such amino acids can be N-terminal, C-terminal or internal to a polypeptide depending upon the location of the exon in an RNA sequence. Deletion of an exon in an RNA also can cause a shift

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in reading frame such that an isoform is produced containing one or more amino acids not present in a wildtype or predominant form of a polypeptide. A shift in reading frame also can result in a stop codon in the reading frame producing an isoform that terminates at a sequence different from that of a wildtype or predominant form of a polypeptide. In one example, a shift of reading frame produces an isoform that is shortened compared to a wildtype or predominant form of a polypeptide. Such shortened isoforms also can contain sequences of amino acids not present in a wildtype or predominant form of a polypeptide.

CSR isoforms also can be produced by exon extension in an RNA. Exon extension is an event of alternative RNA splicing that produces a nucleic acid molecule that contains at least one exon that is greater in length (number of nucleotides contained in the exon) than the corresponding exon in an RNA encoding a wildtype or predominant form of a polypeptide. Additional sequence contained in an exon extension can encode additional amino acids and/or can contain a stop codon that terminates a polypeptide. An exon insertion containing an in-frame stop codon can produce a shortened isoform, that terminates in the sequence of the exon extension. An exon insertion also can shift the reading frame of an RNA, resulting in an isoform containing one or more amino acids not present in a wildtype or predominant form of a polypeptide and/or an isoform that terminates at a sequence different from that of a wildtype or predominant form of a polypeptide. An exon extension can include sequences contained in an intron of an RNA encoding a wildtype or predominant form of a polypeptide and thereby produce an intron fusion protein.

CSR isoforms also can be produced by exon truncation. Exon truncations are RNA molecules that contain a shortening of one or more exons such that the one or more exons are shorter in length (number of nucleotides) compared to a corresponding exon in an RNA encoding a wildtype or predominant form of a polypeptide. An RNA molecule with an exon truncation can produce a polypeptide that is shortened compared to a wildtype or predominant form of a polypeptide. An exon truncation also can result in a shift in reading frame such that an isoform is produced containing one or more amino acids not present in a wildtype or

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predominant form of a polypeptide. A shift in reading frame also can result in a stop codon in the reading frame producing an isoform that terminates at a sequence different from that of a wildtype or predominant form of a polypeptide.

Alternatively spliced RNA molecules including exon modifications can  
5 produce CSR isoforms that lack a domain or a portion thereof sufficient to reduce or remove a biological activity. For example, exon modified RNA molecules can encode shortened CSR polypeptides that lack a domain or portion thereof. Exon modified RNA molecules also can encode polypeptides where a domain is interrupted by inserted amino acids and/or by a shift in reading frame that interrupts a domain  
10 with one or more amino acids not present in a wildtype or predominant form of a polypeptide.

#### **C. Receptor Tyrosine Kinase Isoforms**

CSR isoforms provided herein include isoforms of receptor tyrosine kinases (RTKs), including receptor tyrosine kinase intron fusion proteins. The receptor  
15 tyrosine kinases (RTKs) are a large family of structurally related growth factor receptors. RTKs are involved in cellular processes including cell growth, differentiation, metabolism and cell migration. RTKs also are known to be involved in cell proliferation, differentiation and determination of cell fate. Members of the family include, but are not limited to, epidermal growth factor (EGF) receptors,  
20 platelet-derived growth factor (PDGF) receptors, fibroblast growth factor (FGF) receptors, insulin-like growth factor (IGF) receptors, nerve growth factor (NGF) receptors, vascular endothelial growth factor (VEGF) receptors, receptors to ephrin (termed Eph), hepatocyte growth factor (HGF) receptors (termed MET), TEK/Tie-2 (the receptor for angiopoietin-1), discoidin domain receptors (DDR) and others, such  
25 as Tyro3/Ax1.

Provided herein are RTK isoforms that are modified in one more domains of an RTK such that they lack a domain of an RTK or a portion of a domain sufficient to remove or reduce a biological activity of an RTK. Also provided are RTK isoforms modified at one or more amino acids of an RTK sequence such as by shortening  
30 and/or addition of one more amino acids. Additional amino acids can add a new domain or a portion thereof. RTK isoforms can be modified in a biological activity



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including, but not limited to, dimerization, kinase activity, signal transduction, ligand binding, membrane association and membrane localization. RTK isoforms also can modulate a biological activity of an RTK.

#### 1. RTK Domains and Biological Activities

5 RTKs have a conserved domain structure including an extracellular domain, a membrane-spanning (transmembrane) domain and an intracellular tyrosine kinase domain. The extracellular domain can bind to a ligand, such as a polypeptide growth factor or a cell membrane-associated molecule. Some RTKs have been classified as orphan receptors, having no identified ligand. Some RTKs are classified as  
10 constitutive RTKs, active without ligand binding.

Typically, dimerization of RTKs activates the catalytic tyrosine kinase domain of the receptor and subsequent activities in signal transduction. RTKs can be homodimers or heterodimers. For example, PDGF is a heterodimer composed of  $\alpha$  and  $\beta$  subunits. VEGF receptors are homodimers. EGF receptors can be either  
15 heterodimers or homodimers. In another example, ErbB3, in the presence of the ligand heregulin, heterodimerizes with other members of the ErbB family (EGFR family) such as ErbB2 and ErbB3. Many RTKs are capable of autophosphorylation when dimerized, such as by transphosphorylation between subunits. Autophosphorylation in the kinase domain maintains the tyrosine kinase domain in an  
20 activated state. Autophosphorylation in other regions of the protein can influence interaction of the receptor with other cellular proteins.

RTKs interact in signal transduction pathways. For example, RTKs, when activated can phosphorylate other signaling molecules. For example, EGFR interacts in signal transduction pathways involved in processes including proliferation,  
25 dedifferentiation, apoptosis, cell migration and angiogenesis. EGFR family members can recruit signaling molecules through protein:protein interactions; some interactions involve specific binding of signaling molecules to tyrosine phosphorylated sites on the receptor. For example, the Grb2/Sos complex can bind to phosphotyrosine sites on EGFR, in turn activating the Ras/Raf/MAPK signaling cascade, which influences  
30 cell proliferation, migration and differentiation. Other exemplary signaling molecules include other RTKs, G-coupled receptors, integrins, phospholipase C,

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Ca<sup>2+</sup>/calmodulin-dependent kinases, transcriptional activators, cytokines and other kinases.

## 2. Receptor Tyrosine Kinase Isoforms

RTK isoforms lack a domain or a portion of a domain of a receptor tyrosine kinase. Thus, an RTK isoforms differs from its cognate RTK in one or more  
5 biological activities. In addition, an RTK isoform can modulate a biological activity of an RTK, such as by interacting with an RTK directly or indirectly. Biological activities include, but are not limited to, protein-protein interactions such as dimerization, multimerization and complex formation, specificity and/or affinity for  
10 ligand, cellular localization and relocalization, membrane anchoring, enzymatic activity such as kinase activity, response to regulatory molecules including regulatory proteins, cofactors, and other signaling molecules, such as in a signal transduction pathway.

### RTK isoform structure and activity

15 In one embodiment, an RTK isoform is modified in a kinase domain. For example, an RTK isoform contains a deletion of a kinase domain or a portion thereof. The deletion need not be a deletion of the entire domain, one or more amino acids can be deleted within the domain. The deletion can be at the N-terminus of the kinase domain, the C-terminus or internally within the domain. In another example, an RTK  
20 isoform contains addition of amino acids in a kinase domain. The addition of amino acids can be at the N-terminus of the domain, the C-terminus or anywhere internally within a kinase domain.

In one aspect of the embodiment, kinase activity of an RTK isoform is altered. For example, kinase activity of an RTK isoform is reduced or eliminated. In one  
25 example, substrate specificity of the kinase activity of an RTK isoform is altered. For example, an RTK isoform is capable of autophosphorylation but not phosphorylation of other polypeptides, such as polypeptides in a signal transduction pathway. In another example, an RTK isoform phosphorylates other polypeptides but is not capable of autophosphorylation. Kinase activity of an RTK isoform can be enhanced  
30 in activity. Kinase activity of an RTK isoform can be altered in regulation. For example, the kinase activity can be constitutively active or constitutively inactive, for

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example, unregulated by the addition of ligand, by receptor dimerization, by complexation such as through protein:protein interactions, and/or by autophosphorylation.

In one embodiment, an RTK isoform is modified in a transmembrane domain.

5 For example, an RTK isoform contains a deletion of a transmembrane domain or a portion thereof. The deletion can be at the N-terminus of a transmembrane domain, the C-terminus or internally within the domain. In another example, an RTK isoform contains addition of amino acids in a transmembrane domain. The addition of amino acids can be at the N-terminus of the domain, the C-terminus or anywhere internally  
10 within the transmembrane domain.

In one aspect of the embodiments, membrane association and/or localization of an RTK isoform is altered. For example, an RTK isoform can be a soluble protein (*e.g.* not membrane localized), where a wildtype or a predominant form of the RTK is membrane localized. For example, an RTK isoform can be secreted extracellularly or  
15 localized in the cytoplasm or internally within a cellular organelle. An RTK isoform can be altered in its membrane localization. For example, an RTK isoform can associate with internal membranes, such as membranes of cellular organelles, but not the cytoplasmic membrane. An RTK isoform can be reduced in its association with a membrane, such that the proportion of membrane associated protein is altered; for  
20 example, some of the protein is soluble and some is membrane associated. An RTK isoform also can be altered in the orientation with or within a membrane compared to the orientation of a wildtype or predominant form of an RTK. For example, more or less of the polypeptide can be embedded within the membrane. More or less of the polypeptide can be associated with either side of the cellular membrane. For  
25 example, orientation can be altered such that more of the RTK isoform is found in the cytoplasm or extracellularly compared to a wildtype or predominant form of an RTK.

In one embodiment, an RTK isoform is altered in its dimerization activity. For example, an RTK-isoform homodimerizes (*i.e.* an RTK isoform: RTK isoform complex) but does not heterodimerize or is reduced in heterodimerization with a  
30 wildtype or predominant form of an RTK derived from the same gene. In another example, an RTK- isoform does not homodimerize with itself, or is reduced in

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homodimerization activity but can heterodimerize with a wildtype or predominant form of an RTK from the same gene or a different gene. In another example, an RTK isoform is reduced in heterodimerization with RTKs from other genes but heterodimerizes with RTKs from the same gene.

5           In one embodiment, an RTK isoform is altered in its signal transduction activity. For example, an RTK isoform is altered in its association with other cellular proteins or cofactors in a signal transduction pathway. For example, an RTK isoform is altered in an interaction such as, but not limited to, an interaction with another RTK, a G-coupled receptor, an integrin, phospholipase C, a  $\text{Ca}^{2+}$ /calmodulin-  
10           dependent kinase, a transcriptional activator or regulator, a cytokine and another kinase. In another example, an RTK isoform alters signal transduction of an RTK. For example, an RTK isoform interacts with an RTK and alters its activity in signal transduction, such as by inhibiting or by stimulating signal transduction by the RTK.

          In one embodiment, an RTK isoform is altered in two or more biological  
15           activities. For example, an RTK isoform is altered in kinase activity and membrane association. In another example, an RTK isoform is altered in kinase activity and dimerization. In yet another example, an RTK isoform is altered in kinase activity, dimerization and membrane association. For example, an RTK isoform is  
20           modified in a kinase domain and a transmembrane domain. In another example, insertion of addition of amino acids interrupts the kinase domain and transmembrane domains. In another embodiment, an RTK isoform is modified at a domain junction, or outside the linear sequence of amino acids for a domain and the modification alters a structure, such as the 3-dimensional structure of a domain such as a kinase domain, or a transmembrane domain.

#### 25           **Modulation of RTKs by RTK isoforms**

          RTK isoforms can modulate or alter a biological activity of an RTK, such as by interacting directly or indirectly with an RTK. Biological activities include, but are not limited to, protein-protein interactions such as dimerization, multimerization and complex formation, specificity and/or affinity for ligand, cellular localization and  
30           relocalization, membrane anchoring, enzymatic activity such as kinase activity, response to regulatory molecules including regulatory proteins, cofactors, and other

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signaling molecules, such as in a signal transduction pathway. In one embodiment, interaction of an RTK isoform with an RTK, inhibits an RTK biological activity. In another embodiment, interaction of an RTK isoform with an RTK, stimulates a biological activity of an RTK.

5           For example, an RTK isoform competes with an RTK for ligand binding. An RTK isoform can be employed as a "ligand sponge" to remove free ligand and thereby regulate or modulate the activity of an RTK. In another example, an RTK isoform acts as a negatively acting ligand when heterodimerized or complexed with an RTK, for example, by preventing trans-autophosphorylation. An RTK isoform that  
10       lack the protein kinase domain, or a portion thereof sufficient to alter kinase activity, can inhibit activation of an RTK in a trans dominant manner.

          In one embodiment, an RTK isoform acts as a competitive inhibitor of RTK dimerization. For example, an RTK isoform interacts with an RTK and prevents that RTK from homodimerizing or from heterodimerizing. An isoform that inhibits  
15       receptor dimerization can modulate downstream signal transduction pathways, such as by complexing with the receptor and inhibiting receptor activation as downstream signaling. An RTK isoform also acts as a competitive inhibitor of an RTK by competing directly with an RTK for interactions with other polypeptides and cofactors in a signal transduction pathway.

#### 20       **D.     TNFR isoforms**

          CSR isoforms provided herein include isoforms of tumor necrosis factor receptors (TNFRs). TNFR isoforms lack a domain or a portion of a domain of a TNFR receptor. Thus, a TNFR isoform differs from its cognate TNFR in one or more biological activities. In addition, a TNFR isoform can modulate a biological activity  
25       of a TNFR, such as by interacting with a TNFR directly or indirectly. Biological activities include, but are not limited to, protein-protein interactions such as trimerization, multimerization and complex formation, specificity and/or affinity for ligand, cellular localization and relocalization, membrane anchoring, response to regulatory molecules including regulatory proteins, cofactors, and other signaling  
30       molecules, such as in a signal transduction pathway.

##### **1.     TNFR Domains and Biological Activities**

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The TNF ligand and receptor family regulate a variety of signal transduction pathways including those involved in cell differentiation, activation, and viability. TNFRs have a characteristic repeating extracellular cysteine-rich motif and a variable intracellular domain that differs between members of the TNFR family. The TNFR family of receptors includes, but is not limited to, TNFR1, TNFR2, TNFRp, the low-affinity nerve growth factor receptor, Fas antigen, CD40, CD27, CD30, 4-1BB, OX40, DR3, DR4, DR5, and herpesvirus entry mediator (HVEM). Ligands for TNFRs include TNF- $\alpha$ , lymphotoxin, nerve growth factor, Fas ligand, CD40 ligand, CD27 ligand, CD30 ligand, 4-1BB ligand, OX40 ligand, APO3 ligand, TRAIL and LIGHT. TNFRs include an extracellular domain, including a ligand binding domain, a transmembrane domain and an intracellular domain that participates in signal transduction. These receptors have names. For example, TNFR1 also is referred to as p55 or p60; and TNFR2 also is referred to as p75 or p80. TNFRs are typically trimeric proteins that trimerize at the cell surface. Trimerization is important for biological activity of TNFRs.

TNFRs have a characteristic extracellular domain with a cysteine-rich motif. The extracellular domain includes a ligand binding domain. Typically, each TNFR member binds a unique ligand. A few receptors such as TNFR1 and TNFR2 and DR4 and DR5 have overlapping ligand specificity. TNFRs also trimerize. Trimerization can be induced by ligand interaction. TNFR ligands also can be trimers. Some TNFRs can be proteolytically processed to produce a secreted form of the receptor. The secreted form also trimerizes and retains certain biological activities such as ligand binding, interaction with the membrane bound form of the receptor, and inhibition of the membrane-bound form of the receptor.

TNFRs can trigger signal transduction. For example, TNFR1 activates intracellular pathways involved in apoptosis. TNFR1 trimerizes upon binding TNF ligand. Trimerization induces association of the receptor's death domains. Adapter proteins such as TRADD, TRAF-2, FADD and RIP also associate with the receptor. TRAF-2 and RIP associations activate NF- $\kappa$ B and JNK/AP-1 pathways, including a cascade of kinases. FADD association activates a caspase cascade and subsequent apoptosis.

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## 2. TNFR Isoform structure and activity

In one embodiment, a TNFR isoform is modified in a transmembrane domain. For example, a TNFR isoform contains a deletion of a transmembrane domain or a portion thereof. The deletion can be at the N-terminus of a transmembrane domain, the C-terminus or internally within the domain. In another example, a TNFR isoform contains addition of amino acids in a transmembrane domain. The addition of amino acids can be at the N-terminus of the domain, the C-terminus or anywhere internally within the transmembrane domain.

In one aspect of the embodiments, membrane association and/or localization of a TNFR isoform is altered. For example, a TNFR isoform can be a soluble protein (*e.g.* not membrane localized), where a wildtype or a predominant form of the TNFR is membrane localized. For example, a TNFR isoform can be secreted extracellularly or localized in the cytoplasm or internally within a cellular organelle. A TNFR isoform can be altered in its membrane localization. For example, a TNFR isoform can associate with internal membranes, such as membranes of cellular organelles, but not the cytoplasmic membrane. A TNFR isoform can be reduced in its association with a membrane, such that the proportion of membrane associated protein is altered; for example, some of the protein is soluble and some is membrane associated. A TNFR isoform also can be altered in the orientation with or within a membrane compared to the orientation of a wildtype or predominant form of a TNFR. For example, more or less of the polypeptide can be embedded within the membrane. More or less of the polypeptide can be associated with either side of the cellular membrane. For example, orientation can be altered such that more of a TNFR isoform is found in the cytoplasm or extracellularly compared to a wildtype or predominant form of a TNFR.

In one embodiment, a TNFR isoform is modified in an intracellular domain. For example, a TNFR isoform contains a deletion of an intracellular domain or a portion thereof. The deletion can be at the N-terminus of an intracellular domain, the C-terminus or internally within the domain. In another example, a TNFR isoform contains addition of amino acids in an intracellular domain. The addition of amino

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acids can be at the N-terminus of the domain, the C-terminus or anywhere internally within the intracellular domain.

In one embodiment, a TNFR isoform is altered in its trimerization activity. For example, a TNFR isoform homotrimerizes (*i.e.* a TNFR isoform: TNFR isoform  
5 complex) but does not heterotrimerize or is reduced in heterotrimerization with a wildtype or predominant form of a TNFR derived from the same gene. In another example, a TNFR isoform does not homotrimerize with itself, or is reduced in homotrimerization activity but can heterotrimerize with a wildtype or predominant form of a TNFR from the same gene or a different gene. In one embodiment, a TNFR  
10 isoform acts as a competitive inhibitor of TNFR trimerization. For example, a TNFR interacts with a TNFR and prevents that TNFR from trimerizing.

In one embodiment, a TNFR isoform is altered in its signal transduction activity. For example, a TNFR isoform is altered in its association with other cellular proteins or cofactors in a signal transduction pathway. For example, a TNFR isoform  
15 is altered in an interaction such as, but not limited to, an interaction with a ligand and an adapter protein such as TRADD (TNFR-associated death domain), TRAF-2, FADD (Fas-associated death domain) and RIP (receptor interacting protein). In another example, a TNFR isoform alters signal transduction of a TNFR. For example, a TNFR isoform interacts with a TNFR and alters its activity in signal transduction,  
20 such as by inhibiting or by stimulating signal transduction by the TNFR.

In an exemplary embodiment, a TNFR isoform is altered in two or more biological activities. For example, a TNFR isoform is altered in signal transduction and membrane association. In another example, a TNFR isoform is altered in signal transduction and trimerization. In yet another example, a TNFR isoform is altered in  
25 kinase activity, trimerization and membrane association. In another embodiment, a TNFR isoform is modified in an intracellular domain and a transmembrane domain. For example, the two domains, or a portion of the domains are deleted. In another example, insertion or addition of amino acids interrupts the intracellular domain and transmembrane domains. In another embodiment, a TNFR isoform is modified at a  
30 domain junction, or outside the linear sequence of amino acids for a domain and the



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modification alters a structure, such as the 3-dimensional structure of a domain such as an intracellular domain, or a transmembrane domain.

#### **Modulation of TNFRs by TNFR isoforms**

TNFR isoforms can modulate or alter a biological activity of a TNFR, such as  
5 by interacting directly or indirectly with a TNFR. Biological activities include, but are not limited to, protein-protein interactions such as trimerization, multimerization and complex formation, specificity and/or affinity for ligand, cellular localization and relocalization, membrane anchoring, response to regulatory molecules including regulatory proteins, cofactors, and other signaling molecules, such as in a signal  
10 transduction pathway. In one embodiment, interaction of a TNFR isoform with a TNFR, inhibits a TNFR biological activity. In another embodiment, interaction of a TNFR isoform with a TNFR, stimulates a biological activity of a TNFR.

For example, a TNFR isoform competes with a TNFR for ligand binding. A TNFR isoform can be employed as a "ligand sponge" to remove free ligand and  
15 thereby regulate or modulate the activity of a TNFR. In another example, a TNFR isoform acts as a negatively acting ligand when trimerized or complexed with a TNFR, for example, by preventing signal transduction and/or by inhibiting interaction with a member of a signal transduction pathway, such as adapter proteins. In one embodiment, a TNFR isoform acts as a competitive inhibitor of TNFR trimerization.  
20 For example, a TNFR isoform interacts with a TNFR and prevents that TNFR from trimerizing. An isoform that inhibits receptor trimerization can modulate downstream signal transduction pathways, such as by complexing with the receptor and inhibiting receptor activation as downstream signaling.

#### **E. Methods for identifying and generating CSR Isoforms**

25 CSR isoforms can be generated by analysis and identification of naturally occurring genes and expression products (RNAs) using cloning methods in combination with bioinformatics methods such as sequence alignments and domain mapping and selections.

Provided herein are methods herein for identifying and isolating CSR isoforms  
30 that utilize cloning of expressed gene sequences and alignment with a gene sequence such as a genomic DNA sequence. For example, one or more isoforms can be

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isolated by selecting a candidate gene, such as a receptor tyrosine kinase. Expressed sequences, such as cDNA molecules or regions of cDNAs, are isolated. Primers can be designed to amplify a cDNA or a region of a cDNA. In one example, primers are designed which overlap or flank the start codon of the open reading frame of a candidate gene and primers are designed which overlap or flank the stop codon of the open reading frame. Primers can be used in PCR, such as in reverse transcriptase PCR (RT-PCR) with mRNA, to amplify nucleic acid molecules encoding open reading frames. Such nucleic acid molecules can be sequenced to identify those that encode an isoform. In one example, nucleic acid molecules of different sizes (*e.g.* molecular masses) from a predicted size (such as a size predicted for encoding a wildtype or predominant form) are chosen as candidate isoforms. Such nucleic acid molecules then can be analyzed, such by a method described herein, to further select isoform-encoding molecules having specified properties.

Computational analysis is performed using the obtained nucleic acid sequences to further select candidate isoforms. For example, cDNA sequences are aligned with a genomic sequence of a selected candidate gene. Such alignments can be performed manually or by using bioinformatics programs such as SIM4, a computer program for analysis of splice variants. Sequences with canonical donor-acceptor splicing sites (*e.g.* GT-AG) are selected. Molecules can be chosen which represent alternatively spliced products such as exon deletion, exon retention, exon extension and intron retention can be selected.

Sequence analysis of isolated nucleic acid molecules also can be used to further select isoforms that retain or lack a domain and/or biological function compared to a wildtype or predominant form. For example, isoforms encoded by isolated nucleic acid molecules can be analyzed using bioinformatics programs such as described herein to identify protein domains. Isoforms then can be selected which retain or lack a domain or a portion thereof.

In one embodiment of the method, isoforms are selected that lack a transmembrane domain or portion thereof sufficient to lack or significantly reduce membrane localization. For example, isoforms are selected that are shortened before a transmembrane domain or that are shortened within a transmembrane domain.

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Isoforms also can be selected that lack a transmembrane domain or portion thereof and have one or more amino acids operatively linked in place of the missing domain or portion of a domain. Such isoforms can be the result of alternative splicing events such as exon extension, intron retention, exon deletion and exon insertion. In some  
5 case, such alternatively spliced RNA molecules alter the reading frame of an RNA and/or operatively link sequences not found in an RNA encoding a wildtype or predominant form. Isoforms also can be selected that lack a kinase domain or portion thereof. Isoforms can be selected that lack a kinase domain or portion thereof and also lack a transmembrane domain or portion thereof. Isoforms also can be selected  
10 that lack a multimerization domain, such as a dimerization or trimerization domain, and/or an intracellular domain that interacts with and participates in signal transduction activity.

For example, nucleic acid molecules encoding candidate RTK isoforms can be further selected for isoforms that lack a kinase domain, a transmembrane domain, an  
15 extracellular domain or a portion thereof. Nucleic acid molecules can be selected which encode an RTK isoform and have a biological activity that differs from a wildtype or predominant form of an RTK. In one example, RTK isoforms are selected that lack a transmembrane domain such that the isoforms are not membrane localized and are secreted from a cell. In another example, TNFR isoforms are  
20 identified and selected that lack a transmembrane domain, or a portion thereof. TNFR isoforms also can be selected that lack an intracellular domain or that lack an intracellular domain and a transmembrane domain.

#### **Allelic Variants of Isoforms**

Allelic variants of CSR isoform sequences can be generated or identified that  
25 differ in one or more amino acids from a particular CSR isoform. Allelic variation occurs among members of a population or species and also between species. For example, isoforms can be derived from different alleles of a gene; each allele can have one or more amino acid differences from the other. Such alleles can have conservative and/or non-conservative amino acid differences. Allelic variants also  
30 include isoforms produced or identified from different subjects, such as individual subjects or animal models or other animals. Amino acid changes can result in

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modulation of an isoform biological activity. In some cases, an amino acid difference can be "silent," having no or virtually no detectable effect on a biological activity. Allelic variants of isoforms also can be generated by mutagenesis. Such mutagenesis can be random or directed. For example, allelic variant isoforms can be generated  
5 that alter amino acid sequences or a potential glycosylation site to effect a change in glycosylation of an isoform, including alternate glycosylation, increased or inhibition of glycosylation at a site in an isoform. Allelic variant isoforms can be at least 90% identical in sequence to an isoform. Generally, an allelic variant isoform from the same species is at least 95%, 96%, 97%, 98%, 99% identical to an isoform, typically  
10 an allelic variant is 98%, 99%, 99.5% identical to an isoform.

#### **F. Exemplary CSR Isoforms**

The methods herein can be used to generate CSR isoforms from a variety of genes. One exemplary group of genes is receptor tyrosine kinases. Receptor tyrosine kinases (RTKs) are a large collection of genes and encoded polypeptides that can be  
15 grouped into families based on, for example, structural arrangements of sequence motifs in the polypeptides. For example, structural motifs in the extracellular domains such as, immunoglobulin, fibronectin, cadherin, epidermal growth factor and kringle repeats can be used to group RTKs. Such classification by structural motifs has identified greater than 16 families of RTKs, each with a conserved tyrosine kinase  
20 domain. Examples of RTKs include, but are not limited to, erythropoietin-producing hepatocellular (EPH) receptors (also referred to as ephrin receptors), epidermal growth factor (EGF) receptors, fibroblast growth factor (FGF) receptors, platelet-derived growth factor (PDGF) receptors, vascular endothelial growth factor (VEGF) receptors, cell adhesion RTKs (CAKs), Tie/Tek receptors, hepatocyte growth factor  
25 (HGF) receptors (termed MET), TEK/Tie-2 (the receptor for angiopoietin-1), discoidin domain receptors (DDR), insulin growth factor (IGF) receptors, insulin receptor-related (IRR) receptors and others, such as Tyro3/Ax1. Exemplary genes encoding RTKs include, but are not limited to, ErbB2, ErbB3, DDR1, DDR2, EGFR, EphA1, EphA2, EphA3, EphA 4, EphA 5, EphA 6, EphA 7, EphA8, EphB1, EphB2,  
30 EphB3, EphB4, EphB5, EphB6, FGFR-1, FGFR-2, FGFR-3, FGFR-4, Flt1 (also known as VEGFR-1), VEGFR-2, VEGFR-3 (also known as

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VEGFR), MET, RON, PDGFR-A, PDGFR-B, CSF1R, Flt3, KIT, TIE-1 and TEK (also known as TIE-2) and genes encoding the RTKs noted above and not set forth.

RTKs participate in a variety of signal transduction pathways. RTKs regulate critical cellular processes including cell proliferation, dedifferentiation, apoptosis, cell migration and angiogenesis. RTK activation and thus subsequent activation of a signal transduction pathway is generally dependent on receptor activation, such as by activation of the receptor by ligand binding and autophosphorylation. RTKs can be subject to misregulation leading to misregulation of signal transduction. Such misregulation is associated with a number of diseases and conditions. Alternatively, certain RTKs are expressed on cells and lead to or participate in alteration in cellular activities, such as oncogenic transformation. Such expression and/or misregulation is associated with a number of diseases and conditions, including but not limited to diseases involving abnormal cell proliferation, such as neoplastic diseases, restenosis, disease of the anterior eye, cardiovascular diseases, obesity and a variety of others.

RTK isoforms provided herein and generated by methods provided herein can be used to modulate a biological activity of an RTK, such as an RTK endogenous to a particular cell type or tissue. The ability to modulate a biological activity of an RTK allows re-regulation of misregulated RTKs as well as directed regulation of cellular pathways in which RTKs participate. Modulating a biological activity of an RTK includes direct modulation, whereby an RTK isoform interacts with an RTK, such as by complexation with an RTK, modulation of homodimerization and/or heterodimerization of an RTK and/or modulation of trans-phosphorylation of an RTK, including inhibition of phosphorylation of an RTK. Modulation of an RTK also includes indirect modulation whereby an RTK isoform indirectly affects a biological activity of an RTK. Indirect modulation includes isoforms that act as a "ligand sponge," competing for ligand binding with an RTK. Indirect modulation also includes interactions of an isoform with signaling molecules in a signaling pathway, thus modulating the activity such as by competition with interactions of such signaling molecules with an RTK. Exemplary RTK isoforms and uses of such RTK isoforms in targeting and regulating RTK activity are described below.

#### 1. EGFR

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EGFR (epidermal growth factor receptor) is a 170 kDa protein that binds to EGF, a small, 53 amino acid protein-ligand that stimulates the proliferation of epidermal cells and a variety of other cell types. EGF receptors are widely expressed in epithelial, mesenchymal and neuronal tissues and play important roles in proliferation and differentiation. EGF Receptor is characterized by several functional domains. The EGFR protein (GenBank No. NP\_005219 set forth as SEQ ID NO:252 is characterized by two Receptor L Domains between amino acids 57 – 168 and amino acids 361 – 481. Receptor L Domains make up the bilobal ligand binding site. A Furin-like cysteine rich region, typically involved in the signal transduction mechanism of receptor tyrosine kinases and receptor aggregation, can be found in EGFR between amino acids 184 – 338. The transmembrane domain of EGFR lies between amino acids 646 – 668 and protein kinase domain lies between amino acids 712 – 968.

EGFR polypeptides include allelic variants of EGFR. For example, an allelic variant contains one or more amino acid changes compared to SEQ ID NO:252. For example, one or more amino acid variations can occur in the protein kinase domain of EGFR. An allelic variant can include amino acid changes at position 719 where, for example, G is replaced by C, or at position 858 where, for example, L is replaced by R, or at position 861 where, for example, L is replaced by Q. An allelic variation also can include one or more amino acid changes, such as at position 521 (SNP NO: 11543848) where, for example, R can be replaced by K. In one example, an allelic variant includes one or more amino acid changes compared to SEQ ID NO:252 and the variant exhibits a change in biological activity. Amino acid changes occurring in the protein kinase domain, such as at position 719, 858, or 861, can be associated with a response to Gefitinib in patients with non-small-cell lung cancer indicating an essential role of the EGFR signaling pathway in the tumor, or, such as at position 858, can be associated with enhanced activity of the EGFR receptor in response to EGF as assessed by autophosphorylation of EGFR. An exemplary EGFR allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO: 288.

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EGF receptors are encoded by a family of related genes known as also erbB genes (*e.g.* ErbB2, ErbB3, ErbB4) and HER genes (*e.g.* Her-2). The EGF receptor family includes four members, EGF-receptor (HER-1; ErbB1), human epidermal growth factor receptor-2 (HER-2; ErbB2), HER-3 (ErbB3) and HER-4 (ErbB4). The  
5 ligand for EGFR/HER-1 is EGF, while the ligand for HER-2, HER-3 and HER-4 is neuregulin-1 (NRG-1). NRG-1 preferentially binds to either HER-3 or HER-4 after which the bound receptor subunit heterodimerizes with HER-2. HER-4 also is capable of homodimerization to form an active receptor.

Misregulation of the ErbB family has been implicated in a number of different  
10 types of cancer. For example, overexpression of EGFR is associated with a number of human tumors including, but not limited to, esophageal, stomach, bladder and colon cancers, gliomas and meningiomas, squamous carcinoma of the lungs, and ovarian, cervical and renal carcinomas. Using the methods provided herein, RTK isoforms and pharmaceutical compositions containing RTK isoforms can be generated  
15 for use as therapeutic agents which target and re-regulate misregulation of EGF receptors.

**a. ErbB2**

ErbB2 is a member of the EGF receptor family. The ErbB2 protein (GenBank No. NP\_004439 set forth as SEQ ID NO:266) is characterized by two Receptor L  
20 Domains between amino acids 52 – 173 and amino acids 366 – 486; a Furin-like cysteine rich region between amino acids 189 – 343; the transmembrane domain between amino acids 653 – 675; and protein kinase domain between amino acids 720 – 976. A ligand that binds with high affinity has not been identified for ErbB2. Instead, ErbB3 or ErbB4 when bound by ligand (NRG-1) heterodimerize with ErbB2  
25 to form an active receptor dimer. In addition, ErbB2 exhibits constitutive activity (homodimerization and kinase activity) in the absence of ligand. In addition, overexpression of ErbB2 is capable of cell transformation. ErbB2 overexpression has been identified in a variety of cancers, including breast, ovarian, gastric and endometrial carcinomas. Thus, targeting ErbB2 homodimers can regulate ErbB2  
30 homodimerization. For example, an ErbB2 RTK isoform can target and

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down-regulate ErbB2 overexpression. Additionally, an ErbB2 RTK- isoform can target ErbB3 and/or ErbB4 through heterodimerization.

ErbB2 proteins include allelic variants of ErbB2. In one example, an allelic variant contains one or more amino acid changes compared to SEQ ID NO:266. For example, one or more amino acid variations can occur in the transmembrane domain of ErbB2. An allelic variant can include amino acid changes at position 655 where, for example, I is replaced by V. In one example, an allelic variant includes one or more amino acid changes compared to SEQ ID NO:266 and the variant exhibits a change in a biological activity. Amino acid changes occurring in the transmembrane domain of ErbB2, such as at position 655, can be associated with increased risk of prostate cancer, gastric cancer, or breast cancer. An exemplary ErbB2 allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO: 299.

Provided herein are exemplary ErbB2 isoforms that lack one or more domains or a part thereof compared to a cognate ErbB2 such as set forth in SEQ ID NO:266. Included are exemplary ErbB2 isoforms that lack a transmembrane domain and lack a kinase domain, such as the polypeptides set forth in SEQ ID NOS: 96-98 and 108. Such isoforms can contain other domains of ErbB2. For example, the exemplary ErbB2 isoform set forth as SEQ ID NO: 96 is characterized by two Receptor L Domains between amino acids 54 – 175 and amino acids 368 – 488, and a Furin-like cysteine rich region between amino acids 191 – 345. The exemplary ErbB2 isoform set forth as SEQ ID NOS: 97 and 98 are characterized by two Receptor L Domains between amino acids 52 – 173 and amino acids 366 – 486, and a furin-like cysteine rich region between amino acids 189 – 343. The exemplary ErbB2 isoform set forth as SEQ ID NO: 108 is characterized by a portion of a Receptor L Domain between amino acids 52 – 75.

ErbB2 isoforms can be used to modulate RTKs such as in the treatment of cancers characterized by the overexpression of EGFR receptors such as those characterized by overexpression of ErbB2 and/or ErbB3. ErbB2 isoforms can be used as a treatment for autoimmune diseases which involve EGFR family members in the maintenance of inflammation and hyperproliferation, including asthma. ErbB2



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isoforms also can be used to target RTKs in conditions including Menetrier's disease, Alzheimer's disease and as modulators, for example as an antagonist for bone resorption.

**b. ErbB3**

5 ErbB3 also is a member of the EGF receptor family involved in regulating development of neuronal survival and synaptogenesis, astrocytic differentiation and microglial activation. The ErbB3 protein (GenBank No. NP\_001973 set forth as SEQ ID NO:267) is characterized by two Receptor L Domains between amino acids 55 – 167 and between amino acids 353 – 474; a Furin-like cysteine rich region between  
10 amino acids 180 – 332; transmembrane domain between amino acids 644 – 666; and protein kinase domain between amino acids 709 – 965. The ligand for ErbB3 is NRG-1. Although NRG-1 can bind to ErbB3 and ErbB4, ErbB3 binds NRG-1 with an affinity an order of magnitude lower than ErbB4. ErbB3 has lower tyrosine kinase activity compared to other members of the EGFR family. It is capable of recruiting  
15 alternative signaling molecules, for example, phosphatidylinositol-3 kinase. ErbB3 overexpression has been implicated in a number of human cancers such as breast, lung and bladder cancers and adenocarcinomas.

ErbB3 isoforms can be used to target RTKs such as in the treatment of cancers characterized by the overexpression of EGFR receptors such as those characterized by  
20 overexpression of ErbB2 and/or ErbB3. ErbB3 isoforms can target ErbB3 homodimers. ErbB3 isoforms can target ErbB2 through heterodimerization of an ErbB3 isoform with ErbB2. ErbB3 isoforms can be used for treatment of diseases and conditions in which EGFR receptors are involved. For example, ErbB3 isoforms can be used as a treatment for autoimmune diseases which involve EGFR family  
25 members in the maintenance of inflammation and hyperproliferation, including asthma. ErbB3 isoforms also can be used to target RTKs in conditions including Menetrier's disease, Alzheimer's disease and as modulators, for example as an antagonist for bone resorption.

**2. Discoidin Domain Receptors - DDR1**

30 Discoidin domain receptors (e.g. DDR-1) are a family of RTKs that are thought to play a role in cell adhesion. The DDR1 protein (GenBank No. NP\_054699

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set forth as SEQ ID NO: 250) is characterized by a F5/8 type C domain, also known as the discoidin (DS) domain, between amino acids 46 – 182; the transmembrane domain between amino acids 417 – 439; and protein kinase domain between amino acids 610 – 913. The discoidin domain is a unique structural motif in the extracellular domain that is homologous to the *Dictyostelium discoideum* (slime mold) protein discoidin-1, a carbohydrate-binding protein involved in cell aggregation. The discoidin-like domain, although not found in other RTKs, is found in other extracellular molecules that are known to interact with cellular membrane proteins (e.g., coagulation factors V and VIII).

10       DDR1 proteins include allelic variants of DDR1. In one example, an allelic variant contains one or more amino acid changes compared to SEQ ID NO:250. For example, one or more amino acid variations can occur in the F5/8 type C or discoidin domain of DDR1. An allelic variant can include amino acid changes at position 53 where, for example, W can be replaced by A, or at position 55 where, for example, D  
15       can be replaced by A, or at position 66 where, for example, S can be replaced by A, or at position 68 where, for example, D can be replaced by A, or at position 105 where, for example, R can be replaced by A, or at position 106 where, for example, H can be replaced by A, or at position 110 where, for example, L can be replaced by A, or at position 112 where, for example, K can be replaced by A, or at position 173 where,  
20       for example, V can be replaced by A, or at position 174 where, for example, M can be replaced by A, or at position 175 where, for example, S can be replaced by A. In one example, an allelic variant includes one or more amino acid changes compared to SEQ ID NO:250 and the variant exhibits a change in a biological activity. Amino acid changes occurring in the discoidin domain of DDR1, such as those at position  
25       105 and 175, can result in reduced activation and phosphorylation of DDR1 due to an inability to bind to collagen. Other amino acid changes in the discoidin domain of DDR1, such as those at positions 106, 173, and 174, can result in a marked reduction in the ability of DDR1 to bind to collagen. An exemplary DDR1 allelic variant containing one or more amino acid changes described above is set forth as SEQ ID  
30       NO: 286.

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DDRs are widely expressed in fetal and adult organs and tissues. DDR1 is expressed primarily in epithelial cells in brain, lung, kidney and gastrointestinal tract, whereas DDR2 is expressed in brain, heart, and muscle. DDR also may play an important role in brain development. DDR tyrosine kinases have been linked to human cancers. For example, DDR1 can bind to collagen (*e.g.* types I through VI) and mediate collagen-induced activation of matrix metalloproteinase-1. Matrix metalloproteinase-1 is involved in the degradation of extracellular matrix, which allows neoplastic cells to metastasize. Overexpression of DDR-1 has been linked to cancers such as breast, ovarian and esophageal cancers and a variety of central nervous system neoplasms, such as pediatric brain cancers. Activation of DDR1 also has been implicated in inflammatory responses.

Exemplary DDR isoforms include DDR1 isoforms set forth in SEQ ID NO: 106, 115 and 117. These exemplary DDR1 isoforms lack one or more domains or a part thereof compared to a cognate DDR1 such as set forth in SEQ ID NO:250. The exemplary DDR1 isoforms set forth as SEQ ID NOS: 106, 115, and 117 contain an F5/8 type C domain between amino acids 46 – 182, and lack the transmembrane and protein kinase domains.

DDR1 isoforms, including DDR1 isoforms herein, can include allelic variation in the DDR1 polypeptide. For example, a DDR1 isoform can include one or more amino acid differences present in an allelic variant. In one example, a DDR1 isoform includes one or more allelic variation as set forth in SEQ ID NO:286. Examples of allelic variation include variants in the F5/8 type C and discoidin domains, including, but not limited to amino acid variation at positions corresponding to amino acids 53, 55, 66, 68, 105, 106, 110, 113, 173, 174, or 175 of SEQ ID NO:286.

DDR-1 isoforms can be used to modulate DDR-1 RTK. For example, a DDR-1 isoform can be used to down regulate DDR-1 overexpression and or activation in diseases and conditions in which DDR-1 is involved.

### 3. Eph Receptors

Eph receptors (erythropoietin-producing hepatocellular receptors; also referred to as ephrin receptors) are the largest known family of RTKs. The ligands for Eph receptors are ephrins (Eph receptor interacting protein). The Eph and Ephrin system

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includes at least fourteen Eph receptor tyrosine kinase proteins and nine ephrin membrane ligands. The Eph receptors and Ephrin membrane proteins play important roles in disease and development (see, *e.g.*, Figure 1). For example, binding of cell surface Eph and ephrin proteins results in bi-directional signals that regulate the cytoskeletal, adhesive and motile properties of the interacting cells. Through these signals Eph and Ephrin proteins are involved in early embryonic cell movements, which establish the germ layers, and in cell movements involved in formation of tissue boundaries and the pathfinding of axons. Ligand and receptor are membrane-bound molecules and signaling can occur through either protein. The ephrins have been separated into two classes based on the manner in which they are anchored to the cell membrane; type A ligands are linked to the cell membrane by a glycosylphosphatidylinositol (GPI) linkage and type B ligands encode for a transmembrane domain. Eph receptors include, but are not limited to, EphA1, EphA2, EphA3, EphA4, EphA5, EphA6, EphA7, EphA8, EphB1, EphB2, EphB3, EphB4, EphB5, EphB6.

Ephrin receptors are characterized by a cytoplasmic tyrosine kinase domain, a conserved cysteine-rich domain, two fibronectin type III domains and an immunoglobulin-like N-terminal ligand binding domain. Further, two tyrosine residues near the transmembrane domain are highly conserved and phosphorylated in response to ligand binding and appear to be critical for enzymatic function. Other sites of protein-protein interaction also are mediated by sterile alpha motifs and postsynaptic density protein, disc large, zona occludens binding motifs located near the C-terminal end of some Eph receptors. Sterile alpha motifs (SAM) mediate cell-cell initiated signal transduction via the binding of SH2-containing proteins to a conserved tyrosine that is phosphorylated and in many cases mediates homodimerization.

The Eph family of RTKs is involved in a variety of cellular processes, including embryonic patterning, neuronal targeting, vascular development and angiogenesis. Particularly due to a role in angiogenesis, Eph receptors have been implicated in human cancers, such as breast cancer. Misregulation of EphA receptors also are involved in pathological conditions. For example, upregulation of the EphA

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receptor tyrosine kinase stimulates vascular endothelial cell growth factor (VEGF) - induced angiogenesis, common in certain eye diseases, rheumatoid arthritis and cancer. An EphA isoform, such as an isoform acting as an EphA receptor antagonist can be used to block or inhibit inappropriate angiogenesis. EphB receptors have been implicated in cancers such as colorectal cancers. EphB receptors also play a role in dendritic spine development (post-synaptic targets for excitatory synapses) and may be implicated in neurodegenerative disorders. Exemplary EphA and EphB isoforms are set forth in SEQ ID NOS: 107, 149, 151, 153, 155, 168, 170, 172, and 174.

**a. EphA1**

EphA1 is a type A Eph receptor. The EphA1 protein (GenBank No. NP\_005223 set forth as SEQ ID NO:253) is characterized by an Ephrin ligand binding domain between amino acids 27 – 204, two fibronectin type III domains between amino acids 333 – 431 and between amino acids 448 – 528; a transmembrane domain between amino acids 548 – 570; protein kinase domain between amino acids 624 – 880, and two SAM domains (SAM-1 between amino acids 911 – 975, and SAM-2 between amino acids 910 – 976) at the carboxy terminus.

EphA1 proteins include allelic variants of EphA1. In one example, an allelic variant contains one or more amino acid changes compared to SEQ ID NO:253, such as the allelic variations set forth in SEQ ID NO:289. One or more amino acid variations can occur, for example, in the ephrin ligand binding domain of EphA1, such as an amino acid change at position 160 where, for example, A can be replaced by V.

Type A Eph receptors bind to type A ephrins, which are linked to cell membranes via a GPI anchor. EphA1 is expressed widely in differentiated epithelial cells, including skin, adult thymus, kidney and adrenal cortex. Overexpression of EphA1 has been implicated in a variety of human cancers, including head and neck cancer. EphA1 isoforms can be used to target such diseases and other conditions in which Eph receptors have been implicated.

Exemplary EphA1 isoforms include EphA1 isoforms set forth in SEQ ID NOS: 107, 149, 151, and 153. These exemplary EphA1 isoforms lack one or more domains or a part thereof compared to a cognate EphA1 such as set forth in SEQ ID

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NO:253. The exemplary EphA1 isoforms set forth as SEQ ID NOS:149 and 153 contain an ephrin ligand binding domain between amino acids 27 – 204 and one of two fibronectin type III domains between amino acids 333 – 431. The isoform set forth as SEQ ID NO: 149 lacks a fibronectin type III domain, a transmembrane domain, protein kinase domain, and two SAM domains compared to the cognate receptor. The exemplary EphA1 isoform set forth as SEQ ID NO: 151 contains the ephrin ligand binding domain between amino acids 27 – 204, but does not contain fibronectin type III domains, transmembrane domain, protein kinase domain and SAM domains. The exemplary EphA1 isoform set forth as SEQ ID NO: 107 contains the ephrin ligand binding domain between amino acids 1 – 114, but does not contain fibronectin type III domains, transmembrane domain, protein kinase domain and SAM domains.

EphA1 isoforms, including EphA1 isoforms herein, can include allelic variation in the EphA1 polypeptide. For example, an EphA1 isoform can include one or more amino acid differences present in an allelic variant. In one example, an EphA1 isoform includes one or more allelic variations as set forth in SEQ ID NO:289. An allelic variation can include one or more amino acid changes in the ephrin ligand binding domain, such as at position 160.

#### **b. EphA2**

EphA2 binds ephrin-A3, ephrin-A1, ephrin-A4, an ephrin-A2. EphA2 expression is frequently elevated in cancer and is highly expressed in tumor tissues including breast, prostate, non-small cell lung cancers, colon, kidney, lung, ovary, stomach, uterus, and aggressive melanomas. EphA2 has also been found in Schwann cells, the primitive streak and hindbrain in restricted expression pattern. It has been suggested that EphA2 does not simply function as a marker, but as an active participant in malignant progression. The normal cellular functions of EphA2 are not well understood, but tumor-based models suggests potential roles for EphA2 in the regulation of cell growth, survival, migration, and angiogenesis.

The EphA2 receptor set forth as SEQ ID NO:254 (GenBank No. NP\_004422) is characterized by an ephrin ligand binding domain between amino acids 28 – 201, two fibronectin type III domains between amino acids 329 – 424 and between amino

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acids 436 – 519, a transmembrane domain between amino acids 536 – 558, protein kinase domain between amino acids 613 – 871; and two SAM domains (SAM-1 between amino acids 902 – 966, and SAM-2 between amino acids 901 – 968) at the carboxy terminus.

5 EphA2 proteins include allelic variants of EphA2. In one example, an allelic variant contains one or more amino acid changes compared to positions corresponding to the amino acid sequence set forth as SEQ ID NO:254. For example, one or more amino acid variations can occur in the ephrin ligand binding domain of EphA2. An allelic variant can include amino acid changes at position 94 (SNP NO: 10 1058370) where, for example, I can be replaced by N, or at position 96 (SNP NO: 1058371) where, for example, I can be replaced by F, or at position 99 (SNP NO: 1058372) where, for example, K can be replaced by N. Additional examples of allelic variation can occur in the fibronectin type III domain. An allelic variant can include amino acid changes at position 350 (SNP NO: 11543934) where, for example, P is 15 replaced by T. One or more amino acid variations also can occur in the protein kinase domain. An allelic variant can include amino acid changes at position 825 where, for example, E can be replaced by K. An exemplary EphA2 allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO: 290.

Exemplary EphA2 isoforms lack one or more domains or a part thereof 20 compared to a cognate EphA2 such as set forth in SEQ ID NO:254. The exemplary EphA2 isoform set forth as SEQ ID NO: 168 contains an ephrin ligand binding domain between amino acids 28 – 201, a fibronectin type III domain between amino acids 329 – 424 and a portion of another fibronectin type III domain between amino acids 436 – 497. SEQ ID NO: 168 does not contain the transmembrane, protein 25 kinase, and SAM domains. EphA2 isoforms, including EphA2 isoforms herein, can include allelic variation in the EphA2 polypeptide. For example, an EphA2 isoform can include one or more amino acid difference present in an allelic variant. In one example, an EphA2 isoform includes one or more allelic variations as set forth in SEQ ID NO:290. An allelic variation can include a position corresponding to amino 30 acid positions 94, 96, or 99 in SEQ ID NO:254, or for example, in the fibronectin type

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III domain, such as at a position corresponding to amino acid 350 in SEQ ID NO:254.

**c. EphA8**

EphA8 is a type A Eph receptor. Type A Eph receptors bind to type A  
5 ephrins, which are linked to cell membranes via a GPI anchor. EphA8 has been  
implicated in cell migration and cell adhesion as well as nervous system development,  
including axon guidance. EphA8 isoforms can be used to target such diseases and  
other conditions in which Eph receptors have been implicated.

The EphA8 receptor (GenBank No. NP\_065387 set forth as SEQ ID NO:260)  
10 is characterized by an Ephrin ligand binding domain between amino acids 31 – 204,  
two fibronectin type III domains between amino acids 329 – 425 and amino acids 437  
– 524, a transmembrane domain between amino acids 541 – 563, protein kinase  
domain between 635 – 892 and two SAM domains (SAM-1 between amino acids 931  
– 992 and SAM-2 between amino acids 927 – 994).

15 EphA8 proteins include allelic variants of EphA8. In one example, an allelic  
variant contains one or more amino acid changes compared to positions  
corresponding to the amino acid sequence set forth as SEQ ID NO:260. For example,  
one or more amino acid variations can occur in the fibronectin type III domain of  
EphA8. An allelic variant can include amino acid changes at position 444 (SNP NO:  
20 2295021) where, for example, V can be replaced by M. Allelic variations also can  
occur at position 301 (SNP NO: 638524) where, for example, A can be replaced by V,  
or at position 612 (SNP NO:999765) where, for example, E can be replaced by Q. An  
exemplary EphA8 allelic variant containing one or more amino acid changes  
described above is set forth as SEQ ID NO: 293.

25 **d. EphB1**

EphB1 has been shown to bind to ephrin-B2, ephrin-B1, ephrin-A3, ephrin-A1  
and ephrin-B3. EphB1 is expressed in developing and adult neural tissue. EphB1  
signaling pathways impact responses relevant to vascular development, including cell  
attachment, migration and capillary-like assembly responses.

30 The EphB1 protein (GenBank No. NP\_004432 set forth as SEQ ID NO:261)  
is characterized by an Ephrin ligand binding domain between amino acids 19 – 196,



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two fibronectin type III domains between amino acids 323 – 414 and between amino acids 434 – 518, transmembrane domain between amino acids 541 – 563, protein kinase domain between amino acids 619 – 878, and two SAM domains (SAM-1 between amino acids 909 – 973, and SAM-2 between amino acids 908 – 975) at the carboxy terminus.

EphB1 proteins include allelic variants of EphB1. In one example, an allelic variant contains one or more amino acid changes compared to positions corresponding to the amino acid sequence set forth as SEQ ID NO:261. For example, one or more amino acid variations can occur in the ephrin ligand binding domain of EphB1. An allelic variant can include amino acid changes at position 87 (SNP NO:1042794) where, for example, T can be replaced by S, or at position 152 (SNP NO:1042793) where, for example, G can be replaced by R. Additional examples of amino acid changes can occur in the fibronectin type III domain. An allelic variant can include amino acid changes at position 367 (SNP NO:1042789) where, for example, R is replaced by G, or at position 485 (SNP NO:1042788) where, for example, R is replaced by S. One or more amino acid changes also can occur in the protein kinase domain. An allelic variant can include amino acid changes at position 813 (SNP NO:1042786) where, for example, V can be replaced by I, or at position 847 (SNP NO:1042785) where, for example, M can be replaced by T. Another example of amino acid changes can occur in the SAM domain. An allelic variant can include amino acid changes at position 973 (SNP NO:1042784) where, for example, R is replaced by W. Allelic variations also can occur at position 274 (SNP NO:1126906) where, for example, T is replaced by R. An exemplary EphB1 allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO: 294.

Exemplary EphB1 isoforms lack one or more domains or a part thereof compared to a cognate EphB1 such as set forth in SEQ ID NO:261. The exemplary EphB1 isoform set forth as SEQ ID NO: 155 contains a portion of an ephrin ligand binding domain between amino acids 19 – 167 and lacks fibronectin type III domains, transmembrane domain, protein kinase domain, and SAM domains compared with a cognate EphB1 receptor (e.g. SEQ ID NO:261).

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EphB1 isoforms, including EphB1 isoforms herein, can include allelic variation in the EphB1 polypeptide. For example an EphB1 isoform can include one or more amino acid differences present in an allelic variant. In one example, an EphB1 isoform includes one or more allelic variation as set forth in SEQ ID NO:294.

- 5 An allelic variation can include one or more amino acid changes in the ephrin ligand binding domain, such as positions corresponding to amino acid positions 87 and 152 of SEQ ID NO:261.

**e. EphB4**

- 10 EphB4 receptors bind to ephrin-B2 and ephrin-B1 proteins. Ephrin-B proteins transduce signals, such that bidirectional signaling can occur upon interaction with Eph receptor.

- The EphB4 receptor polypeptide (GenBank No. NP\_004435 set forth as SEQ ID NO:264) is characterized by an ephrin ligand binding domain between amino acids 17 – 197, two fibronectin type III domains between amino acids 324 – 414 and  
15 between amino acids 434 – 519, transmembrane domain between amino acids 541 – 563, cytoplasmic protein kinase domain between 615 – 874, and two SAM domains (SAM-1 between amino acids 905 – 969, and SAM-2 between amino acids 904 – 971) at the carboxy terminus.

- EphB4 proteins can include allelic variants of EphB4. In one example, an  
20 allelic variant contains one or more amino acid changes compared to SEQ ID NO:264. For example, one or more amino acid variations can occur in the fibronectin type III domain of EphB4. An allelic variant can include amino acid changes at position 463 (SNP NO:7457245) where, for example, A can be replaced by D, or at position 471 (SNP NO:3891495) where, for example, Y can be replaced by D.  
25 Additional amino acid changes can occur in the SAM domain. An allelic variant can include amino acid changes at position 926 (SNP NO:1056997) where, for example, E can be replaced by D. An exemplary EphB4 allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO: 297.

- Exemplary EphB4 isoforms include the EphB4 isoforms set forth in SEQ ID  
30 NO: 170, 172 and 174. These exemplary EphB4 isoforms lack one or more domains or a part thereof compared to a cognate EphB4 such as set forth in SEQ ID NO:264.

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The exemplary EphB4 isoform set forth as SEQ ID NO: 170 contains an ephrin ligand binding domain between amino acids 17 – 197. SEQ ID NO: 170 does not contain fibronectin type III domains, transmembrane domain, protein kinase domain, and SAM domains. The exemplary EphB4 isoform set forth as SEQ ID NO: 172 contains an ephrin ligand binding domain between amino acids 17 – 197, a fibronectin type III domain between amino acids 324 – 414 and a portion of another fibronectin type III domain between amino acids 434 – 514. SEQ ID NO: 172 does not contain the transmembrane domain, protein kinase domain, and SAM domains. The exemplary EphB4 isoform set forth as SEQ ID NO: 174 contains an ephrin ligand binding domain between amino acids 17 – 197 and a portion of a fibronectin type III domain between amino acids 324 – 413. SEQ ID NO: 174 does not contain the second fibronectin type III domain, transmembrane domain, protein kinase domain, and SAM domains.

EphB4 isoforms, including EphB4 isoforms herein, can include allelic variation in the EphB4 polypeptide. For example an EphB4 isoform can include one or more amino acid differences present in an allelic variant. In one example, an EphB4 isoform includes one or more allelic variation as set forth in SEQ ID NO:297. An allelic variation can include one or more amino acid changes in the fibronectin type III domain, such as at positions corresponding to amino acid positions 463 or 471 of SEQ ID NO:264.

#### **4. Fibroblast Growth Factor Receptors**

The fibroblast growth factor receptor (FGFR) family includes FGFR-1, FGFR-2, FGFR-3, FGFR-4 and FGFR-5. There are at least 23 known FGF proteins that are capable of binding to one or more FGF receptors. FGF receptors are structurally characterized by three N-terminal Ig-like domains (extracellular), a transmembrane domain and the split tyrosine-kinase domain at the C-terminus (cytoplasmic). FGFs and their receptors are involved in stimulation of cellular proliferation, promoting angiogenesis and wound healing, and modulating cell motility and differentiation. FGFRs have been implicated in a variety of human cancers as well as diseases of the eye.

##### **a. FGFR-1**

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FGFR-1 has specificity for FGF-1, -2, and -4 and is expressed in a number of cell types including fibroblasts, endothelial cells, certain epithelial cells, vascular smooth muscle cells, lymphocytes, macrophages, and numerous tumor cells.

The FGFR-1 polypeptide (GenBank No. AAA35835 set forth as SEQ ID  
5 NO:268) is characterized by three immunoglobulin-like domains; domain 1 between amino acids 35 – 119, domain 2 between amino acids 156 – 246, and domain 3 between amino acids 253 – 357. FGFR-1 also has a transmembrane domain between amino acids 375 – 397 and protein kinase domain between amino acids 476 – 752.

FGFR-1 proteins include allelic variants of FGFR-1. In one example, an  
10 allelic variant contains one or more amino acid changes compared to positions corresponding to the amino acid sequence set forth as SEQ ID NO:268. For example, one or more amino acid variations can occur in the immunoglobulin domain of FGFR-1. An allelic variant can include amino acid changes at position 97 where, for example, G can be replaced by D, or at position 99 where, for example, Y can be  
15 replaced by C, or at position 165 where, for example, A can be replaced by S, or at position 190 where, for example, K can be replaced by E, or at position 192 where, for example, S can be replaced by G, or at position 198 where, for example, D can be replaced by G, or at position 275 where, for example, C can be replaced by Y. Additional amino acid changes can occur in the protein kinase domain. An allelic  
20 variant can include amino acid changes at position 605 where, for example, V can be replaced by M, or at position 664 where, for example, W can be replaced by R, or at position 717 where, for example, M can be replaced by R. One or more amino acid change also can occur at position 22 where, for example, R can be replaced by S, or at position 250 where, for example P can be replaced by R, or at position 770 where, for  
25 example, P can be replaced by S, or at position 816 where, for example G can be replaced by R, or at position 820 where, for example, R can be replaced by C. In one example, an allelic variant includes one or more amino acid change compared to SEQ ID NO:268 and the variant exhibits a change in a biological activity. Polypeptides containing amino acid changes in either the immunoglobulin or protein kinase domain  
30 of FGFR-1, such as those at positions 97, 99, 165, 275, 605, 664, or 717, can be characterized as loss-of function mutations. In the context of a cognate receptor (such

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as SEQ ID NO: 268) such changes cause autosomal dominant Kallmann syndrome. Amino acid changes occurring in the protein kinase domain, such as at position 717, can impair PLC gamma association with the receptor and inhibit FGF-mediated phosphatidylinositol and Ca<sup>2+</sup> mobilization; these changes, however, do not affect  
5 FGF-mediated mitogenesis. Additional allelic variants, such as at position 250, can be associated with autosomal dominant skeletal disorders such as Pfeiffer syndrome. An exemplary FGFR-1 allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO:300.

Exemplary FGFR-1 isoforms include FGFR-1 isoforms set forth in SEQ ID  
10 NOS: 119 and 176. These exemplary FGFR-1 isoforms lack one or more domains or a part thereof compared to a cognate FGFR-1 such as set forth in SEQ ID NO:268. The exemplary FGFR-1 isoform set forth as SEQ ID NO: 119 contains immunoglobulin-like domain 2 between amino acids 67 – 157 and a portion of immunoglobulin-like domain 3 between amino acids 164 – 220. The exemplary  
15 FGFR-1 isoform set forth as SEQ ID NO: 176 contains immunoglobulin-like domain 2 between amino acids 70 – 159 and immunoglobulin-like domain 3 between amino acids 166 – 268. These exemplary isoforms each lack the transmembrane and protein kinase domains compared to a cognate FGFR-1 polypeptide (e.g. SEQ ID NO:268).

FGFR-1 isoforms, including FGFR-1 isoforms herein, can include allelic  
20 variation in the FGFR-1 polypeptide. For example, a FGFR-1 isoform can include one or more amino acid differences present in an allelic variant. In one example, a FGFR-1 isoform includes one or more allelic variation as set forth in SEQ ID NO:300. An allelic variant can include one or more amino acid change in the immunoglobulin domain, such as at positions corresponding to amino acid positions  
25 97, 99, 165, 190, 192, and 198 of SEQ ID NO:268. An additional allelic variant can include one or more amino acid changes at a position corresponding to amino acid position 22 of SEQ ID NO:268.

#### **b. FGFR-2**

FGFR-2 is a member of the fibroblast growth factor receptor family. Ligands  
30 to FGFR-2 include a number of FGF proteins, such as, but not limited to, FGF-1 (basic FGF), FGF-2 (acidic FGF), FGF-4 and FGF-7. FGF receptors are involved in

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cell-cell communication of tissue remodeling during development as well as cellular homeostasis in adult tissues. Overexpression of, or mutations in, FGFR-2 have been associated with hyperproliferative diseases, including a variety of human cancers, including breast, pancreatic, colorectal, bladder and cervical malignancies. FGFR-2 isoforms such as FGFR-2 intron fusion proteins can be used to treat conditions in which FGFR-2 is upregulated, including cancers.

The FGFR-2 protein (GenBank No. NP\_000132 set forth as SEQ ID NO:269) is characterized by three immunoglobulin-like domains; domain 1 between amino acids 41 - 125, domain 2 between amino acids 159 - 249, and domain 3 between amino acids 256 - 360. FGFR-2 also contains a transmembrane domain between amino acids 378 - 400 and protein kinase domain between amino acids 481 - 757.

FGFR-2 proteins include allelic variants of FGFR-2. In one example, an allelic variant contains one or more amino acid changes compared to SEQ ID NO:269. For example, one or more amino acid variations can occur in the immunoglobulin domain of FGFR-2. An allelic variant can include amino acid changes at position 105 where, for example Y can be replaced by C, or at position 162 where, for example, M can be replaced by T, or at position 172 where, for example, A can be replaced by F, or at position 186 (SNP NO: 755793) where, for example, M can be replaced by T, or at position 267 where, for example, S can be replaced by P, or at position 276 where, for example, F can be replaced by V, or at position 278 where, for example, C can be replaced by F, or at position 281 where, for example, Y can be replaced by C, or at position 289 where, for example, Q can be replaced by P, or at position 290 where, for example, W can be replaced by C, or at position 315 where, for example, A can be replaced by S, or at position 338 where, for example, G can be replaced by R, or at position 340 where, for example, Y can be replaced by H, or at position 341 where, for example, T can be replaced by P, or at position 342 where, for example, C can be replaced by R, Y, S, F, or W, or at position 344 where, for example, A can be replaced by P or G, or at position 347 where, for example, S can be replaced by C, or at position 351 where, for example, S can be replaced by C, or at position 354 where, for example, S can be replaced by C. Further examples of amino acid changes can occur in the transmembrane domain. An allelic variant can

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include amino acid changes at position 384 where, for example, G can be replaced by R. Additional amino acid changes also can occur in the protein kinase domain. An allelic variant can include amino acid changes at position 549 where, for example, N can be replaced by H, or at position 565 where, for example, E can be replaced by G, or at position 641 where, for example, K can be replaced by R, or at position 659 where, for example, K can be replaced by N, or at position 663 where, for example, G can be replaced by E, or at position 678 where, for example, R can be replaced by G. Allelic variations also can occur at position 6 where, for example, R can be replaced by P, or at position 31 where, for example, T can be replaced by I, or at position 152 where, for example, R can be replaced by G, or at position 252 where, for example, S can be replaced by W or L, or at position 253 where, for example, P can be replaced by S or R, or at position 372 where, for example, S can be replaced by C, or at position 375 where, for example, Y can be replaced by C. In one example, an allelic variant includes one or more amino acid change compared to SEQ ID NO:269 and the variant exhibits a change in a biological activity. Amino acid changes occurring in the immunoglobulin domain, such as at positions 105, 172, 267, 276, 278, 281, 289, 290, 315, 338, 340, 341, 342, 344, 347, 351, 354, or the protein kinase domain, such as at positions 549, 565, 641, 659, 663, or 678, or other amino acid changes, such as at positions 252, 253, or 375, are associated with syndromic craniosynostosis including Apert, Crouzon, or Pfeiffer syndromes when such amino acid changes are present in a cognate FGFR-2 such as set forth in SEQ ID NO: 269. An exemplary FGFR-2 allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO: 301.

Exemplary FGFR-2 isoforms include FGFR-2 isoforms set forth in SEQ ID NOS: 178, 180, 182 and 184. These exemplary FGFR-2 isoforms lack one or more domains or a part thereof compared to a cognate FGFR-2 such as set forth in SEQ ID NO:269. The exemplary FGFR-2 isoform set forth as SEQ ID NO: 184 contains three immunoglobulin-like domains; domain 1 between amino acids 41 – 125, domain 2 between amino acids 159 – 249 and domain 3 between amino acids 256 – 360, but lacks transmembrane and protein kinase domains. The exemplary FGFR-2 isoform set forth as SEQ ID NO: 180 contains the immunoglobulin-like domains 1, 2 and a

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portion of domain 3 (between amino acids 41 – 125, 159 – 249 and 256 – 313, respectively), but is missing transmembrane and protein kinase domains. The exemplary FGFR-2 isoform set forth as SEQ ID NO: 178 contains immunoglobulin-like domain 1 between amino acids 41 – 125 and domain 2 between amino acids 159 – 249, but lacks immunoglobulin-like domain 3, and transmembrane and protein kinase domains. The exemplary FGFR-2 isoform set forth as SEQ ID NO: 182 contains immunoglobulin-like domains 2 between amino acids 44 – 134 and domain 3 between amino acids 141 – 245, but does not contain an immunoglobulin-like domain 1, a transmembrane domain and protein kinase domain.

10 FGFR-2 isoforms, including FGFR-2 isoforms herein, can include allelic variation in the FGFR-2 polypeptide. For example, a FGFR-2 isoform can include one or more amino acid differences present in an allelic variant. In one example, a FGFR-2 isoform includes one or more allelic variation as set forth in SEQ ID NO:301. An allelic variation can include one or more amino acid changes in the  
15 immunoglobulin domain, such as at positions 105, 162, 172, 186, 267, 276, 278, 281, 289, 290, 315, 338, 340, 341, 342, 344, 347, 351, or 354. Additional allelic variations can include one or more amino acid changes, such as at positions 6, 31, 152, 252, or 253.

**c. FGFR-4**

20 FGFR-4 is a member of the FGF receptor tyrosine kinase family. FGFR-4 regulation is modified in some cancer cells. For example, in some adenocarcinomas FGFR-4 is down-regulated compared with expression in normal fibroblast cells. Alternate forms of FGFR-4, are expressed in some tumor cells. For example, ptd-FGFR-4 lacks a portion of the FGFR-4 extracellular domain but contains the third Ig-  
25 like domain, a transmembrane domain and a kinase domain. This isoform is found in pituitary gland tumors and is tumorigenic. FGFR-4 isoforms can be used to treat diseases and conditions in which FGFR-4 is misregulated. For example, an FGFR-4-isoform can be used to down regulate tumorigenic FGFR-4 isoforms such as ptd-FGFR-4.

30 The FGFR-4 protein (GenBank No. NP\_002002 set forth as SEQ ID NO: 271) is characterized by three immunoglobulin – like domains; domain 1 between amino



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acids 35 – 113, domain 2 between amino acids 152 – 242, and domain 3 between amino acids 249 – 351. FGFR-4 also contains a transmembrane domain between amino acids 370 – 386 and protein kinase domain between amino acids 467 – 743.

5 FGFR-4 proteins include allelic variants of FGFR-4. In one example, an allelic variant contains one or more amino acid changes compared to SEQ ID NO:271. For example, one or more amino acid variations can occur in the immunoglobulin domain of FGFR-4. An allelic variant can include amino acid changes at position 275 (SNP NO: 11954456) where, for example, S is replaced by R, or at position 297 (SNP NO:1057633) where, for example, D is replaced by V.

10 Additional amino acid changes can occur in the protein kinase domain. An allelic variant can include an amino acid change at position 616 (SNP NO:2301344) where, for example, R can be replaced by L. Allelic variations also can occur at position 10 (SNP NO: 1966265) where, for example, V can be replaced by I, or at position 136 (SNP NO: 376618) where, for example, P can be replaced by L, or at position 388

15 (SNP NO: 351855) where, for example, G can be replaced by R. An exemplary FGFR-4 allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO: 303.

Exemplary FGFR-4 isoforms lack one or more domains or a part thereof compared to a cognate FGFR-4 such as set forth in SEQ ID NO:271. Exemplary

20 FGFR-4 isoforms include FGFR-4 isoforms set forth in SEQ ID NOS: 91, 109 and 121. The exemplary FGFR-4 isoform set forth as SEQ ID NO: 121 contains immunoglobulin-like domain 1 between amino acids 35 – 113, domain 2 between amino acids 152 – 242, and domain 3 between amino acids 249 – 351, but lacks a transmembrane and protein kinase domains. The exemplary FGFR-4 isoform set

25 forth as SEQ ID NO: 109 contains immunoglobulin-like domain 2 between amino acids 62 – 154 and a portion of domain 3 between amino acids 161 – 209, but does not contain an immunoglobulin – like domain 1, a transmembrane and protein kinase domains. The exemplary FGFR-4 isoform set forth as SEQ ID NO: 91 lacks the immunoglobulin – like domains, the transmembrane domain and the protein kinase

30 domain present in the cognate receptor (e.g. SEQ ID NO:271).

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FGFR-4 isoforms, including FGFR-4 isoforms herein, can include allelic variation in the FGFR-4 polypeptide. For example, a FGFR-4 isoform can include one or more amino acid differences present in an allelic variant. In one example, a FGFR-4 isoform includes one or more allelic variation as set forth in SEQ ID

5 NO:303. An allelic variation can include one or more amino acid changes in the immunoglobulin domain, such as at amino acids corresponding to positions 275 or 297 of SEQ ID NO:271. Additional allelic variants can include one or more amino acid changes, such as at amino acids corresponding to amino acid positions 10 or 136 of SEQ ID NO:271.

10 **5. Platelet-Derived Growth Factor Receptors**

Platelet-derived growth factor receptors (PDGFRs) are homo or heterodimers that contain two subunits,  $\alpha$  and  $\beta$ . Receptor subunits are comprised of five Ig-like domains at the N-terminus, a transmembrane domain, and a split kinase domain at the C-terminus.

15 The PDGFR-A protein (GenBank No. NP\_006197 set forth as SEQ ID NO: 275) is characterized by three immunoglobulin – like domains; domain 1 between amino acids 42 – 102, domain 2 between amino acids 228 – 292, and domain 3 between amino acids 319 – 412. PDGFR-A also contains a transmembrane domain between amino acids 527 – 549 and protein kinase domain between amino acids 593 –  
20 953. The PDGFR-B protein (GenBank No. NP\_002600 set forth as SEQ ID NO: 276) is characterized by two immunoglobulin – like domains between amino acids 32 – 119 and amino acids 213 – 311, a transmembrane domain between amino acids 534 – 556, and protein kinase domain between amino acids 600 – 958.

PDGF receptors can include allelic variation, for example, PDGFR-B and  
25 PDGFR-A allelic variants. In one example, an allelic variant contains one or more amino acid changes compared to SEQ ID NOS:275 or 276. For example, with respect to PDGFR-B, allelic variations can include one or more amino acid change at position 29 (SNP NO:17110944) where, for example, I is replaced by F, or at position 194 (SNP NO:2229560) where, for example, I is replaced by T, or at position 345 (SNP  
30 NO:2229558) where, for example, P is replaced by S. An exemplary PDGFR-B

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allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO: 307.

PDGF receptors and ligands are involved in a variety of cellular processes, including clot formation, extracellular matrix synthesis, chemotaxis of immune cells  
5 apoptosis and embryonic development. Overexpression of PDGF receptors has been linked to a number of human carcinomas, including stomach, pancreas, lung and prostate. Activation of the platelet derived growth factor receptor (PDGFR) is associated with benign prostatic hypertrophy and prostate cancer as well as other cancer types. Activation of PDGF-R also is associated with smooth muscle  
10 proliferation in development of atherosclerosis. PDGFR also has been implicated in modulating proliferative vitreoretinopathy, a common medical problem caused by the proliferation of fibroblastic cells behind the retina, resulting in retinal detachment. Similar to its receptor, PDGF ligand is a homo or heterodimer of A and/or B chains. The  $\alpha$ -PDGF receptor can be activated by either PDGF-A or PDGF-B. A  $\beta$ -PDGF  
15 receptor only can be activated by the PDGF-B chain. Two additional members of the PDGF family also have been isolated, PDGF-C and PDGF-D.

Exemplary PDGFR isoforms include the isoforms set forth in SEQ ID NO:111 and 147. These exemplary PDGFR isoforms lack one or more domains or a part thereof compared to a cognate PDGFR such as set forth in SEQ ID NO:276. The  
20 exemplary PDGFR-A isoform set forth as SEQ ID NO: 111 is characterized by one immunoglobulin – like domains between amino acids 41 – 102, but does not contain a transmembrane domain or protein kinase domain. The exemplary PDGFR-B isoform set forth as SEQ ID NO: 147 is characterized by two immunoglobulin – like domains between amino acids 32 – 119 and amino acids 213 – 310, but does not contain  
25 transmembrane domain or protein kinase domain.

PDGFR isoforms, including PDGFR isoforms herein, can include allelic variation in the PDGFR polypeptide. For example, a PDGFR isoform can include one or more amino acid differences present in an allelic variant. In one example, a PDGFR isoform includes one or more allelic variation as set forth in SEQ ID NO:307.  
30 An allelic variation can include one or more amino acid changes, such as at amino acids corresponding to positions 29 or 194 of SEQ ID NO:276.

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PDGFR isoforms can be used to target diseases and conditions in which PDGFR is involved, including hyperproliferative diseases, such as proliferative vitreoretinopathy and smooth muscle hyperproliferative conditions including atherosclerosis.

5           Flt3 (fms-related tyrosine kinase 3), CSF1R (colony stimulating factor 1 receptor) and KIT (receptor for c-kit) also are members of the PDGFR RTK subfamily. The CSF1R protein (GenBank No. NP\_005202 set forth as SEQ ID NO: 249) is characterized by three immunoglobulin – like domains; domain 1 between amino acids 19 – 102, domain 2 between amino acids 202 – 324, and domain 3  
10 between amino acids 412 – 487. CSF1R also is characterized by a transmembrane domain between amino acids 515 – 537 and protein kinase domain between amino acids 582 – 910. CSF1R proteins include allelic variants of CSF1R. In one example, an allelic variant contains one or more amino acid changes compared to a cognate CSF1R receptor such as set forth in SEQ ID NO:249. For example, one or more  
15 amino acid variations can occur in the immunoglobulin-like domain 2 of CSF1R. An allelic variant can include one or more amino acid changes as position 279 (SNP NO: 3829986) where, for example, V can be replaced by M. Allelic variants also can include amino acid changes at position 362 (SNP NO:10079250) where, for example, H can be replaced by R, or position 969 (SNP NO:1801271 where, for example, Y  
20 can be replaced by C. An exemplary CSF1R allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO: 285.

          The exemplary CSF1R isoform set forth as SEQ ID NO: 145 contains an immunoglobulin – like domain 1 between amino acids 19 – 102, a partial immunoglobulin – like domain 2 between amino acids 202 – 296. SEQ ID NO: 145  
25 does not contain Ig-like domain 3, a transmembrane or protein kinase domain. CSF1R isoforms, including CSF1R isoforms herein, can include allelic variation in the CSF1R polypeptide. For example, a CSF1R isoform can include one or more amino acid differences present in an allelic variant. In one example, a CSF1R isoform includes one or more allelic variation as set forth in SEQ ID NO:285. An allelic  
30 variation can include one or more amino acid changes in the immunoglobulin-like

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domain 2, such as at positions 279. Allelic variations also can include one or more amino acid changes, such as at position 362.

The KIT receptor (GenBank No. NP\_000213 set forth as SEQ ID NO:273) is characterized by an immunoglobulin – like domain between amino acids 210 – 336, a transmembrane domain between amino acids 521 – 543, and protein kinase domain between amino acids 589 – 924. KIT receptor include allelic variants of KIT. In one example, an allelic variant contains one or more amino acid changes compared to SEQ ID NO:273, such as set forth in SEQ ID NO:305. For example, one or more amino acid variations can occur in the transmembrane domain of KIT. An allelic variant can include one or more amino acid changes at position 541 (SNP NO: 3822214)) where, for example, M can be replaced by L or V. Additional examples of amino acid changes can occur in the protein kinase domain. An allelic variant can include one or more amino acid changes at position 664 where, for example, G can be replaced by R, or at position 788 where, for example C can be replaced by R, or at position 801 where, for example, T can be replaced by I, or at position 816 where, for example, D can be replaced by V, H, or Y, or at position 820 where, for example, D is replaced by V, or at position 822 where, for example, N can be replaced by K or Y, or at position 823 where, for example, Y can be replaced by D or C, or at position 835 where, for example, W can be replaced by R, or at position 869 where, for example, P can be replaced by S, or at position 900 where, for example, Y can be replaced by F. Allelic variants also can include one or more amino acid change at position 52, where, for example, D is replaced by N, or at position 136 where, for example, C is replaced by R, or at position 178 where, for example, A is replaced by T, or at position 557 where, for example, W is replaced by R.

In one example, an allelic variant includes one or more amino acid changes compared to SEQ ID NO:273 and the variant exhibits a change in a biological activity. For example, an allelic variant contains one or more amino acid changes occurring in the protein kinase domain of KIT, such as at positions 816, 823, 822, or 801. In another example, one or more amino acid changes occur in the protein kinase domain, such as at position 900, and are associated with diminished receptor phosphorylation, association with adaptor proteins such as CrkII, and activation. In

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the context of a wildtype or predominant form of the receptor such allelic variation can be associated with a disease or condition, for example, testicular seminomas, intracranial germinomas, chronic myelogenous leukemia, human peibaldism and idiopathic myelofibrosis.

5           The exemplary KIT isoform set forth as SEQ ID NO: 93 contains an immunoglobulin – like domain between amino acids 210 – 336, but does not contain a transmembrane domain or protein kinase domain. KIT isoforms, including KIT isoforms herein, can include allelic variation in the KIT polypeptide. For example, a KIT isoform can include one or more amino acid differences present in an allelic  
10       variant. In one example, a KIT isoform includes one or more allelic variations as set forth in SEQ ID NO:305. An allelic variation can include one or more amino acid changes, such as at amino acids corresponding to positions 136 or 178 of SEQ ID NO:273.

          The Flt3 receptor (GenBank No. NP\_004110 set forth as SEQ ID NO:272) is  
15       characterized by an immunoglobulin-like domain between amino acids 78 – 161 and between amino acids 257 – 345, a transmembrane domain between amino acids 542 – 564, and a tyrosine kinase domain between amino acids 610 – 943. Flt3 proteins include allelic variants of Flt3. In one example, an allelic variant contains one or more amino acid changes compared to SEQ ID NO:272, such as those set forth in  
20       SEQ ID NO:304. For example, one or more amino acid variations can occur in the tyrosine kinase domain of Flt3. An allelic variant can include amino acid changes at position 835 where, for example, D can be replaced by Y, H, or F, or at position 836 where, for example, I can be replaced by S, or at position 841 where, for example, N can be replaced by I or Y, or at position 842 where, for example Y can be replaced by  
25       H. In one example, an allelic variant includes one or more amino acid changes compared to SEQ ID NO:272 and the variant exhibits a change in a biological activity. One or more amino acid changes occurring in the tyrosine kinase domain of Flt3 receptor, such as at positions 835 or 841, can result in the constitutive activation of downstream targets of Flt3, such as signal transducer and activator of transcription  
30       STAT5, in the absence of Flt3 ligand stimulation. One or more amino acid changes can be present in the tyrosine kinase domain of Flt3, such as at positions 835, 836,

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and 842, also can be associated with a disease or condition, for example the progression from myelodysplastic syndrome to acute myeloid leukemia in infants and adults.

Flt3 is expressed in placenta and various adult tissues such as gonads, brain  
5 and in hematopoietic cells. Flt3 is associated with biological regulation in gonads, brain and nervous systems. Flt3 has been implicated as a target for pediatric cancers such as pediatric AML. KIT is involved in regulation in a broad variety of cell types including erythroid cells, interstitial cells, mast cells and germ cells. KIT is associated with a variety of cancers including gastrointestinal stromal tumors. RTK isoforms of  
10 Flt3, CSF1R and KIT can be used in the treatment of diseases and conditions in which the RTK are involved.

#### 6. MET (Receptor for hepatocyte growth factor)

MET is a RTK for hepatocyte growth factor (HGF), a multifunctional cytokine controlling cell growth, morphogenesis and motility. HGF, a paracrine factor  
15 produced primarily by mesenchymal cells, induces mitogenic and morphogenic changes, including rapid membrane ruffling, formation of microspikes, and increased cellular motility. Signaling through MET can increase tumorigenicity, induce cell motility and enhance invasiveness *in vitro* and metastasis *in vivo*. MET signaling also can increase the production of protease and urokinase, leading to extracellular  
20 matrix/basal membrane degradation, which are important for promoting tumor metastasis.

MET is a RTK that is highly expressed in hepatocytes. MET is comprised of two disulfide-linked subunit, a 50-kD  $\alpha$  subunit and a 145-kD  $\beta$  subunit. In the fully processed MET protein, the  $\alpha$  subunit is extracellular, and the  $\beta$  subunit has  
25 extracellular, transmembrane, and tyrosine kinase domains. The ligand for MET is hepatocyte growth factor (HGF). Signaling through FGF and MET stimulates mitogenic activity in hepatocytes and epithelial cells, including cell growth, motility and invasion. As with other RTKs, these properties link MET to oncogenic activities. In addition to a role in cancer, MET also has been shown to be a critical factor in the  
30 development of malaria infection. Activation of MET is required to make

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hepatocytes susceptible to infection by malaria, thus MET is a prime target for prevention of the disease.

The MET receptor (GenBank No. NP\_000236 set forth as SEQ ID NO:274) is characterized by a Sema domain between amino acids 55 – 500. In addition to  
5 hepatocyte growth factor receptor, the Sema domain occurs in semaphorins, which are a large family of secreted and transmembrane proteins, some of which function as repellent signals during axon guidance. In MET, the Sema domain has been shown to be involved in receptor dimerization in addition to ligand binding. The MET protein also is characterized by a plexin cysteine rich repeat between amino acids 519 – 562,  
10 three IPT/TIG domains between amino acids 563 – 655, amino acids 657 – 739 and amino acids 742 – 836. IPT stands for Immunoglobulin-like fold shared by Plexins and Transcription factors. TIG stands for the Immunoglobulin-like domain in transcription factors (Transcription factor IG). TIG domains in MET likely play a role in mediating some of the interactions between extracellular matrix and receptor  
15 signaling. The MET protein also is characterized by a transmembrane domain between amino acids 951 – 973 and cytoplasmic protein kinase domain between amino acids 1078 – 1337.

MET receptors include allelic variants of MET. In one example, an allelic variant contains one or more amino acid changes compared to SEQ ID NO:274. For  
20 example, one or more amino acid variations can occur in the Sema domain of MET. An allelic variant can include amino acid changes at position 113 where, for example, K is replaced by R, or at position 114 where, for example, D is replaced by N, or at position 145 where, for example, V is replaced by A, or at position 148 where, for example, H is replaced by R, or at position 151 where, for example, T is replaced by  
25 P, or at position 158 where, for example, V is replaced by A, or at position 168 where, for example, E is replaced by D, or at position 193 where, for example, I is replaced by T, or at position 216 where, for example, V is replaced by L, or at position 237 where, for example, V is replaced by A, or at position 276 where, for example, T is replaced by A, or at position 314 where, for example, F is replaced by L, or at  
30 position 337 where, for example, L is replaced by P, or at position 340 where, for example, D is replaced by V, or at position 382 where, for example, N is replaced by



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D, or at position 400 where, for example, R is replaced by G, or at position 476 where, for example, H is replaced by R, or at position 481 where, for example, L is replaced by M, or at position 500 where, for example, D is replaced by G. In a further example, one or more amino acid variation can occur in the plexin cysteine rich repeat domain of MET. An allelic variant can include amino acid changes at position 542 where, for example, H can be replaced by Y. In other examples, one or more amino acid variation can occur in the IPT/TIG domains of MET. An allelic variant can include amino acid changes at position 622 where, for example, L is replaced by S, or at position 720 where, for example, F is replaced by S, or at position 729 where, for example, A is replaced by T. In an additional example, one or more amino acid variations can occur in the protein kinase domain of MET. An allelic variant can include amino acid changes at position 1094 where, for example, H is replaced by R or at position 1100 where, for example, N is replaced by Y or at position 1230 where, for example, Y is replaced by C, or at position 1235 where, for example, Y is replaced with D, or at position 1250 where, for example, M is replaced by T. Allelic variants also can include one or more amino acid changes, such as at position 37 where, for example, V is replaced by A, or at position 39 where, for example M is replaced by T, or at position 42 where, for example, Q is replaced by R, or at position 501 where, for example, Y can be replaced by H, or at position 511 where, for example, T can be replaced by A. In one example, an allelic variant includes one or more amino acid changes compared to SEQ ID NO:274 and the variant exhibits a change in a biological activity. An exemplary MET allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO: 306. Amino acid changes occurring in the tyrosine kinase domain of MET receptor, such as those described above, can be associated with dysregulated function of MET. For example, in the context of a wildtype or predominant form of the receptor, allelic changes in MET receptor are implicated in the development of human cancer including the promotion of tumor invasion, angiogenesis, and metastasis.

Exemplary isoforms of MET provided herein lack one or more domains or a part thereof compared to a cognate MET receptor such as set forth in SEQ ID NO:274. Exemplary MET receptor isoforms provided herein (*e.g.* SEQ ID NOS:

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103, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, and 214) lack a transmembrane domain and/or a protein kinase domain. In addition, exemplary MET isoforms provided herein contain one or more domains of a wildtype or predominant form of MET receptor (e.g. set forth as SEQ ID NO:274). For example, MET receptor isoforms set forth as SEQ ID NOS: 103, 190, 192, 196, 198, 200, 202, 204, 206, 208, 210, 212, and 214 all contain complete Sema domains. MET isoforms set forth as SEQ ID NOS: 103, 192, 196, 198, 200, 202, 206, 208, 210, 212, and 214 contain complete plexin cysteine rich repeat domains. Met receptor isoforms can include one or more IPT/TIG domains. For example, MET receptor isoforms set forth as SEQ ID NOS: 103, 198, 200, 202, 204, 206, 208, 210, 212, and 214 contain at least one complete IPT/TIG domain. MET receptor isoforms set forth as SEQ ID NOS: 103, 208, 210, 212, and 214 all contain at least two complete IPT/TIG domains. MET receptor isoforms set forth as SEQ ID NOS: 103 and 212 contain three complete IPT/TIG domains. Among the MET receptor isoforms provided herein are isoforms that contain a portion of a domain compared to a wildtype or predominant form of MET receptor (e.g. set forth as SEQ ID NO:274). For example, MET receptor isoforms set forth as SEQ ID NOS: 186, 188, and 194 contain portions of the Sema domain between amino acids 55 – 412, 55 – 468, and 55 – 400, respectively. The MET receptor isoform set forth as SEQ ID NO: 196 contains a portion of an IPT/TIG domain between amino acids 563 – 621. MET receptor isoforms set forth as SEQ ID NOS: 198, 200 and 204, in addition to the one full IPT/TIG domain, contain a portion of a second IPT/TIG domain (between amino acids 657 – 664, 657 – 719, and 629 – 672, respectively). The MET receptor isoform set forth as SEQ ID NO: 210, in addition to the two full IPT/TIG domains, contains a portion of a third IPT/TIG domain between amino acids 742 – 823.

MET isoforms, including MET isoforms herein, can include allelic variation in the MET polypeptide. For example, a MET isoform can include one or more amino acid differences present in an allelic variant. In one example, a MET isoform includes one or more allelic variations as set forth in SEQ ID NO:306. An allelic variation can include one or more amino acid change in the Sema domain, such as at positions 113, 114, 145, 148, 151, 158, 168, 193, 216, 237, 276, 314, 337, 340, 382, 400, 476, 481,

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481, or 500. Allelic variations also can occur in the plexin cysteine rich repeat domain, such as at position 542. Further allelic variations also can occur in the IPT/TIG domain, such as at positions 622, 720, or 729. Allelic variations also can include other amino acid changes, such as at positions 37, 39, 42, 501, or 511.

5 MET isoforms can be used in treating or preventing metastatic cancer, and in inhibiting angiogenesis, such as angiogenesis necessary for tumor growth. Therapeutic applications of MET isoforms include lung cancer, malignant peripheral nerve sheath tumors (MPNST), colon cancer, gastric cancer, and cutaneous malignant melanoma.

10 MET isoforms also can be used in combination with other anti-angiogenesis drugs to prevent tumor cell invasiveness. Anti-angiogenesis drugs produce a state of hypoxia in tumors which can promote tumor cell invasion by sensitizing cells to HGF stimulation. MET isoforms can target and modulate biological activity of MET, such as by inhibiting or down-regulating MET when, anti-angiogenesis drugs are given,  
15 thus preventing or inhibiting tumor cell invasiveness.

Therapeutic applications of MET isoforms also include prevention of malaria. Plasmodium, the causative agent of malaria, must first infect hepatocytes to initiate a mammalian infection. Sporozoites migrate through several hepatocytes, by breaching their plasma membranes, before infection is finally established in one of them.  
20 Wounding of hepatocytes by sporozoite migration induces the secretion of hepatocyte growth factor (HGF), which renders hepatocytes susceptible to infection. Infection depends on activation of the HGF receptor, MET, by secreted HGF. The malaria parasite exploits MET as a mediator of signals that make the host cell susceptible to infection. HGF/MET signaling induces rearrangements of the host-cell actin  
25 cytoskeleton that are required for the early development of the parasites within hepatocytes. MET- isoforms can be administered as a therapeutic to downregulate MET, thus inhibiting or preventing induction of MET signaling by malaria parasite and therefore inhibiting or preventing malaria infection.

RON (recepteur d'origine nantais; also known as macrophage stimulating 1  
30 receptor) is another member of the MET subfamily of RTKs. A ligand for RON is macrophage-stimulating protein (MSP). RON is expressed in cells of epithelial

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origin. RON plays a role in epithelial cancers including lung cancer and colon cancers. RON and MET are expressed in ovarian cancers and are suggested to confer a selective advantage to cancer cells, thus promoting cancer progression. RON also is overexpressed in certain colorectal cancers. Germline mutations in the RON gene  
5 have been linked to human tumorigenesis. RON isoforms can be used to modulate RON, such as by modulating RON activity in diseases and conditions where RON is overexpressed.

The RON protein (GenBank No. NP\_002438 set forth as SEQ ID NO:277) is characterized by a Sema domain between amino acids 58 – 507, a plexin cysteine rich  
10 domain between amino acids 526 – 568, three IPT/TIG domains (between amino acids 569 – 671, amino acids 684 – 767, and amino acids 770 – 860), a transmembrane domain between amino acids 960 – 982 and cytoplasmic protein kinase domain between amino acids 1082 – 1341.

RON receptors include allelic variants of RON. In one example, an allelic  
15 variant contains one or more amino acids changes compared to SEQ ID NO:277, such as those set forth in SEQ ID NO:308. For example, one or more amino acid variations can occur in the Sema domain of RON. An allelic variant can include single nucleotide polymorphisms (SNP) at position 113 (SNP No. 3733136) where, for example, G is replaced by S, or at position 209 where, for example, G is replaced  
20 by A, or at position 322 (SNP No. 2230593) where, for example, Q is replaced by R, or at position 440 (SNP No. 2230592) where, for example, N is replaced by S. An amino acid variation also can occur at position 523 (SNP No. 2230590) where, for example, R is replaced by Q, or at position 946 (SNP No. 13078735) where, for example V is replaced by M. Additionally, one or more amino acid variations can  
25 occur in the protein kinase domain of RON. An allelic variant can include amino acid changes at position 1195 (SNP No. 7433231) where, for example, G is replaced by S, or at position 1335 (SNP No. 1062633) where, for example, R is replaced by G, or at position 1232 where, for example, D is replaced by V, or at position 1254 where, for example, M is replaced by T. In one example, an allelic variant includes one or more  
30 amino acid changes compared to SEQ ID NO:277 and the variant exhibits a change in a biological activity. Allelic variants, for example in the context of a wildtype or

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predominant form of the receptor, can be associated with a disease or condition. For example, amino acid changes occurring in the tyrosine kinase domain of RON, such as at positions corresponding to 1232 and 1254 of SEQ ID NO:277, can be associated with oncogenic cell transformation and tumor development by causing cellular accumulation of b-catenin whereby increases in the levels of b-catenin are associated with cancer.

SEQ ID NOS: 129, 216, 218 and 220 set forth exemplary RON isoforms. Exemplary RON isoforms lack one or more domains or a part thereof compared to a cognate RON such as set forth in SEQ ID NO:277. For example, exemplary RON isoforms set forth as SEQ ID NOS: 129, 216, 218 and 220 lack a transmembrane domain and protein kinase domain. The exemplary RON isoform set forth as SEQ ID NO:129 is characterized by a truncated Sema domain between amino acids 58 – 495. SEQ ID NO: 129 does not contain the plexin cysteine rich domain and IPT/TIG domains. The exemplary RON isoform set forth as SEQ ID NO: 216 also is characterized by a truncated Sema domain between amino acids 58 – 410, a complete plexin cysteine rich domain between amino acids 420 – 462, and a portion of an IPT/TIG domain between amino acids 463 – 521. The exemplary RON isoform set forth as SEQ ID NO: 220 contains complete Sema and plexin cysteine rich domains as well as a portion of an IPT/TIG domain between amino acids 569 – 627. SEQ ID NO: 218 sets forth an exemplary RON isoform that contains a complete Sema domain, plexin cysteine rich domain, and three IPT/TIG domains.

RON isoforms, including RON isoforms herein, also can include allelic variation in the RON polypeptide. For example a RON isoform can include one or more amino acid differences present in an allelic variant. In one example, a RON isoform includes one or more allelic variations as set forth in SEQ ID NO:308. An allelic variant can include one or more amino acid changes in the Sema domain, such as at positions 113, 209, 322. or 440. An allelic variant also can include one or more amino acid change, such as at position 523.

#### **7. Vascular endothelial growth factor (VEGF)**

The vascular endothelial growth factor (VEGF) is a family of closely related growth factors with a conserved pattern of eight cysteine residues and sharing

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common VEGF receptors. VEGF receptors include VEGFR-1 (Flt-1) VEGFR-2 (Flk-1/KDR), and VEGFR-3 (Flt-4). Ligands for VEGF receptors include vascular endothelial growth factor-A (also known as vasculotropin (VAS) or vascular permeability factor (VPF)) VEGF-B, VEGF-C, VEGF-D and placental growth factor (PlGF). The VEGF proteins and receptors play an important role in many aspects of angiogenesis, including cell migration, proliferation and tube formation, thus linking these proteins to the pathogenesis of many types of cancer. Flt-1, Flk, and Flt-4/KDR are genes encoding VEGFR family members.

Exemplary RTK- isoforms for targeting VEGFR-related diseases and conditions include VEGFR isoforms set forth in SEQ ID NOS: 99-102, 110, 123, 125, 127, 224 and 226. Such isoforms can be used in the treatment of acute inflammatory disease, such as Kawasaki disease, rheumatoid arthritis, diabetic retinopathy, retinopathy and psoriasis, as well as re-regulation of abnormal angiogenesis. Additionally VEGFR- isoforms can be used for treatment of cancers including breast carcinoma.

**a. VEGFR-1 (Flt-1)**

Flt-1 (*fms*-like tyrosine kinase-1) is a member of the VEGF receptor family of tyrosine kinases. Ligands for Flt-1 include VEGF-A and PlGF (placental growth factor). Since Flt-1 and its ligands are important for angiogenesis, dysregulation of these proteins have significant impacts on a variety of diseases stemming from abnormal angiogenesis, such as proliferation or metastasis of solid tumors, rheumatoid arthritis, diabetic retinopathy, retinopathy and psoriasis. Flt-1 also has been implicated in Kawasaki disease, a systemic vasculitis with microvascular hyperpermeability.

The VEGFR-1 polypeptide set forth as SEQ ID NO:282 (GenBank No. NP\_002010) is characterized by four immunoglobulin – like domains; domain 1 between amino acids 231 – 337, domain 2 between 332 – 427, domain 3 between amino acids 558 – 656, and domain 4 between amino acids 661 – 749. VEGFR-1 also contains a transmembrane domain between amino acids 764 – 780 and protein kinase domain between amino acids 827 – 1154.

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SEQ ID NOS: 99-102, 110 and 123 set forth exemplary VEGFR-1 isoforms. The exemplary VEGFR-1 isoforms lack one or more domains or a part thereof compared to a cognate VEGFR-1 such as set forth in SEQ ID NO:282. For example, the exemplary VEGFR-1 isoforms lack a transmembrane domain and protein kinase domain compared to a cognate VEGFR-1 (e.g. SEQ ID NO:282). Such isoforms also can lack additional domains or portions of domains of a cognate VEGFR-1. The exemplary VEGFR-1 isoforms set forth as SEQ ID NOS: 99, 100 and 110 contain two immunoglobulin – like domains between amino acids 231 – 337 and between amino acids 332 – 427, but do not contain immunoglobulin-like domains 2 and 3. The exemplary VEGFR-1 isoform set forth as SEQ ID NO: 101 contains immunoglobulin – like domain 1 between amino acids 231 – 337 and a portion of immunoglobulin – like domain 2 between amino acids 332 – 394. The exemplary VEGFR-1 isoform set forth as SEQ ID NO: 102 contains a portion of one immunoglobulin – like domain between amino acids 231 – 331. VEGFR-1 isoforms, including VEGFR-1 isoforms herein, can include allelic variation in the VEGFR-1 polypeptide, such as one or more amino acid changes compared to a cognate VEGFR-1 polypeptide (e.g., SEQ ID NO: 282).

**b. VEGFR-2 (KDR/Flk-1)**

VEGFR-2 (KDR/Flk-1) is a member of the VEGF receptor family of tyrosine kinases. Ligands for VEGFR-2 includes VEGF. VEGF interacts with its receptors, VEGFR-2 and VEGFR-1, expressed on endothelial and hematopoietic stem cells, and thereby promotes recruitment of these cells to neo-angiogenic sites, accelerating the revascularization process. As such, VEGF is found in several types of tumors and has a tumoral angiogenic activity *in vitro* and *in vivo*. The interaction of VEGF with VEGFR-1 mediates cell migration whereas the interaction of VEGF with VEGFR-2 mediates cell proliferation. The VEGFR-2 receptor is the main human receptor responsible for the VEGF activity in physiological and pathological vascular development, and VEGF-KDR signaling pathway is a potential target for the development of anti- and pro- angiogenic agents.

The VEGFR-2 protein (GenBank No. NP\_002244 set forth as SEQ ID NO:283) is characterized by three immunoglobulin – like domains; domain 1 between

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amino acids 224 – 325, domain 2 between amino acids 333 – 418, and domain 3 between amino acids 666 – 766. VEGFR-2 also contains a transmembrane domain between amino acids 763 – 785 and protein kinase domain between amino acids 834 – 1160.

5 VEGFR-2 proteins include allelic variants of VEGFR-2. In one example, an allelic variant contains one or more amino acids changes compared to SEQ ID NO: 283. For example, one or more amino acid variations can occur in the immunoglobulin-like domain of VEGFR-2. An allelic variant can include single nucleotide polymorphisms (SNP) at position 297 (SNP No: 2305948) where, for  
10 example, V can be replaced by I, or at position 349 (SNP No: 1824302) where, for example, R can be replaced by K, or at position 392 (SNP No: 2034964) where, for example, D can be replaced by N. Additionally, one or more amino acid variations can occur in the protein kinase domain of VEGFR-2. An allelic variant can include amino acid changes at position 835 (SNP No: 1139775) where, for example, K is  
15 replaced by N, or at position 848 (SNP No: 1139776) where, for example, V is replaced by E, or at position 952 (SNP No: 13129474) where, for example, V is replaced by I. One or more amino acid changes also can occur in the transmembrane domain. An allelic variant can include amino acid changes at position 772 (SNP No: 1062832) where, for example A is replaced by T. An amino acid variation also can  
20 occur at position 472 (SNP No: 1870377) where, for example, Q is replaced by H, or at position 787 (SNP No: 1139774) where, for example, R is replaced by G, or at position 1147 where, for example, P is replaced by S, or at position 1210 (SNP No: 11540507) where, for example, P is replaced by I, or at position 1347 (SNP No: 1139777) where, for example, S is replaced by T. In one example, an allelic variant  
25 includes one or more amino acid changes compared to SEQ ID NO:283 and the variant exhibits a change in biological activity. Allelic variants, for example in the context of a wildtype or predominant form of the receptor, can be associated with a disease or condition. For example, amino acid changes occurring in the kinase domain of VEGFR-2, such as at position 1147 described herein, can be associated  
30 with tumors such as those found in Juvenile hemangiomas. An exemplary VEGFR-2



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allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO: 313.

Exemplary isoforms of VEGFR-2 include isoforms lacking one or more domains or a part thereof compared to a cognate VEGFR-2 such as set forth in SEQ ID NO:283. Such isoforms include the isoform set forth in SEQ ID NO: 224 that does not contain transmembrane or protein kinase domains. The exemplary VEGFR-2 isoform set forth as SEQ ID NO:224 is characterized by immunoglobulin – like domains between amino acids 224 – 325, amino acids 333 – 418, and a portion of a third immunoglobulin – like domain between amino acids 666 – 691.

VEGFR-2 isoforms, including VEGFR-2 isoforms herein, can include allelic variation in the VEGFR-2 polypeptide. For example a VEGFR-2 isoform can include one or more amino acid differences present in an allelic variant. In one example, a VEGFR-2 isoform includes one or more allelic variations as set forth in SEQ ID NO:313. An allelic variant can include one or more amino acid changes in the immunoglobulin-like domain, such as at positions 297, 349, or 392. Allelic variants also can include one or more amino acid change such as at position 472.

### **c. VEGFR-3**

VEGFR-3 is expressed predominantly in lymphatic endothelial cells. VEGFR-3 signaling is crucial for development and maintenance of lymphatic vessels. Mouse models expressing VEGFR-3 can be used to assess effects on lymphatic tissue development and maintenance in the presence of VEGFR-3 isoforms. VEGFR-3 also can have effects on blood vascular endothelium.

The VEGFR-3 polypeptide (GenBank No. NP\_002011 set forth as SEQ ID NO:284) is characterized by four immunoglobulin – like domains; domain 1 between amino acids 231 – 328, domain 2 between amino acids 349 – 398, domain 3 between amino acids 571 – 655 and domain 4 between amino acids 677 – 766. VEGFR-3 also contains a transmembrane domain between amino acids 776 – 798 and protein kinase domain between amino acids 845 – 1169.

VEGFR-3 polypeptides include allelic variants of VEGFR-3. In one example, an allelic variant contains one or more amino acids changes compared to SEQ ID NO: 284. For example, one or more amino acid variations can occur in the protein kinase

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domain of VEGFR-3. An allelic variant can include single nucleotide polymorphisms (SNP) at position 854 where, for example, G can be replaced by S, or at position 890 (SNP No: 448012) where, for example, Q can be replaced by H, or at position 915 where, for example, A can be replaced by P, or at position 916 where, for example, C and be replaced by W, or at position 933 where, for example, G can be replaced by R, or at position 954 where, for example, P can be replaced by S, or at position 1008 where, for example, P can be replaced by L, or at position 1041 where, for example, R can be replaced by W or Q, or at position 1137 where, for example, P can be replaced by L, or at position 1164 (SNP No: 1049080) where, for example, D can be replaced by E. An amino acid variation also can occur at position 24 where, for example, D is replaced by G, or at position 134 where, for example, D is replaced by G, or at position 149 where, for example, N can be replaced by D, or at position 494 (SNP No: 307826) where, for example T can be replaced by A, or at position 1189 (SNP No: 744282) where, for example, R can be replaced by C. In one example, an allelic variant includes one or more amino acid changes compared to SEQ ID NO:284 and the variant exhibits a change in a biological activity. Amino acid changes occurring in the tyrosine kinase domain can interfere with VEGFR-3 signaling, such as those described herein at positions 854, 915, 916, 933, 1041, and 1137. Allelic variants, for example in the context of a wildtype or predominant form of the receptor can be associated with a disease or condition. For example, amino acid changes occurring in the tyrosine kinase domain can be associated with primary congenital lymphoedema; amino acid changes at position 954 can be associated with tumors such as juvenile hemangiomas. An exemplary VEGFR-3 allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO: 314.

Exemplary VEGFR-3 isoforms lack one or more domains or a part thereof compared to a cognate VEGFR-3 such as set forth in SEQ ID NO:284. SEQ ID NOS: 125, 127 and 226 set forth exemplary VEGFR-3 isoforms that lack a transmembrane and protein kinase domains. Such isoforms contain other domains of VEGFR-3. The exemplary VEGFR-3 isoform set forth as SEQ ID NO:226 is characterized by immunoglobulin – like domain 1 between amino acids 231 – 328, domain 2 between amino acids 349 – 398, domain 3 between amino acids 571 – 655, and a portion of a

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domain 4 between amino acids 677 – 723. SEQ ID NO: 127 is characterized by one immunoglobulin – like domain between amino acids 231 – 272.

VEGFR-3 isoforms, including VEGFR-3 isoforms herein, also can include allelic variation in the VEGFR-3 polypeptide compared to a cognate VEGFR-3 receptor such as set forth in SEQ ID NO:284. For example a VEGFR-3 isoform can include one or more amino acid differences present in an allelic variant such as set forth in SEQ ID NO:314, for example at positions corresponding to amino acid position 24, 134, 149 or 494 of SEQ ID NO:284.

#### 8. TIE

Tie-1 and Tie-2/TEK (tyrosine kinase with immunoglobulin-like and EGF-like domains) receptors are endothelial RTKs with immunoglobulin and epidermal growth factor homology domains. Exemplary RTK- isoforms for targeting Tie/TEK receptors include RTK isoforms set forth in SEQ ID NO: 104, 105, 112, 113, 131, 133, 135, 137, 139, 141, 143 and 222. Such RTK isoforms can be used for treatment of diseases and conditions in which the Tie/Tek receptor is implicated, including anti-angiogenesis therapy in diseases such as cancer, eye diseases, and rheumatoid arthritis. Other diseases and conditions that can be treated with TIE/TEK isoforms include inflammatory diseases such as arthritis, rheumatism, and psoriasis, benign tumors and preneoplastic conditions, myocardial angiogenesis, hemophilic joints, scleroderma, vascular adhesions, atherosclerotic plaque neovascularization, telangiectasia, and wound granulation. Additional targets for TEK receptor isoforms include diseases in which TEK is overexpressed, for example, chronic myeloid leukemia.

##### a. Tie-1

Tie-1 is a receptor tyrosine kinase that plays an essential role in vascular development and angiogenesis where it is thought to be required for vessel maturation and stabilization. Tie-1 also acts as an antiapoptotic survival signal. Tie-1 expression is associated with endothelial cells and neovascularization and physically associates with the related receptor TEK. Tie-1 also is expressed in a variety of tumors and metastases including lung and breast and also is involved in thyroid

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tumorigenesis. Tie-1 is strongly induced during wound healing. The ligands responsible for activating Tie-1 remain unidentified.

The Tie-1 receptor set forth as SEQ ID NO:279 (GenBank No. NP\_005415 set forth as SEQ ID NO: 279) is characterized by two immunoglobulin domains between  
5 amino acids 139 – 197 and amino acids 365 – 428, an EGF domain between amino acids 224 – 255, a laminin EGF-like domain between amino acids 231 – 272, three fibronectin type III domains (between amino acids 446 – 533, amino acids 546 – 632, and amino acids 644 – 729), transmembrane domain between amino acids 764 – 786, and cytoplasmic protein kinase domain between 839 – 1107.

10 Tie-1 proteins include allelic variants of Tie-1. In one example, an allelic variant contains one or more amino acids changes compared to SEQ ID NO: 279. For example, one or more amino acid variations can occur in the immunoglobulin domain of Tie-1. An allelic variant can include single nucleotide polymorphisms (SNP) at position 142 (SNP No: 11545380) where, for example, A can be replaced by T. An  
15 amino acid variation also can occur at position 1109 (SNP No: 6698998) where, for example, R is replaced by C. An exemplary Tie-1 allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO: 310.

Exemplary Tie-1 isoforms lack one or more domains or a part thereof compared to a cognate Tie-1 such as set forth in SEQ ID NO:279. For example, the  
20 exemplary Tie-1 isoforms provided herein lack transmembrane and protein kinase domains. Such exemplary Tie-1 isoforms include the Tie-1 isoforms set forth in SEQ ID NOS:113, 135, 137, 139, 141, 143 and 222. These isoforms contain other domains of the Tie-1 receptor. The exemplary Tie-1 isoform set forth as SEQ ID NOS: 113 and 222 are characterized by two immunoglobulin domains between amino acids 139  
25 – 197 and amino acids 365 – 428, an EGF domain between amino acids 224 – 255, a laminin EGF-like domain between amino acids 231 – 272, and three fibronectin type III domains (between amino acids 446 – 533, amino acids 546 – 632, and amino acids 644 – 729). The exemplary Tie-1 isoforms set forth as SEQ ID NOS: 137, 141 and 143 contain an immunoglobulin domain between amino acids 139 – 197, an EGF  
30 domain between amino acids 224 – 255 and a laminin EGF-like domain between

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amino acids 231 – 272. The exemplary Tie-1 isoforms set forth as SEQ ID NOS: 135 and 139 contain at least a portion of the immunoglobulin domain.

Tie-1 isoforms, including Tie-1 isoforms herein, can include allelic variation in the Tie-1 polypeptide. For example, a Tie-1 isoform can include one or more  
5 amino acid differences compared to a cognate Tie-1 receptor (e.g. SEQ ID NO:279). In one example, a Tie-1 isoform includes one or more allelic variations as set forth in SEQ ID NO:310. For example, an allelic variant of a Tie-1 isoform can include an amino acid change in the immunoglobulin domain, such as at position 142.

**b. Tie-2 (TEK)**

10 The known ligands for Tie-2/TEK include angiopoietin (Ang)-1 and Ang-2. These RTKs play an important role in the development of the embryonic vasculature and continue to be expressed in adult endothelial cells. Tie-2/TEK is a RTK that is expressed almost exclusively by vascular endothelium. Expression of Tie-2/TEK is important for the development of the embryonic vasculature. Overexpression and/or  
15 mutation of Tie-2/TEK has been linked to pathogenic angiogenesis, and thus tumor growth, as well as myeloid leukemia.

The Tie-2/TEK protein (GenBank No. NP\_000450 set forth as SEQ ID NO:278) is characterized by a laminin EGF-like domain between amino acids 219 – 268, three fibronectin type III domains (between amino acids 444 – 529, amino acids  
20 543 – 626, and amino acids 639 – 724), a transmembrane domain between amino acids 748 – 770, and cytoplasmic protein kinase domain between amino acids 824 – 1092.

TEK proteins include allelic variants of TEK. In one example, an allelic variant contains one or more amino acids changes compared to SEQ ID NO: 278. For  
25 example, one or more amino acid variations can occur in fibronectin type III domain of TEK. An allelic variant can include single nucleotide polymorphisms (SNP) at position 486 (SNP No: 1334811) where, for example, V can be replaced by I, or at position 695 where, for example, I can be replaced by T, or at position 724 (SNP No. 4631561) where, for example, A can be replaced by T. An allelic variant also can  
30 occur in the protein kinase domain of TEK. An allelic variant can include amino acid changes at position 849 where, for example, R can be replaced by W. An amino acid

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variation also can occur at position 346 where, for example, P can be replaced by Q. In one example, an allelic variant includes one or more amino acid changes compared to SEQ ID NO:278 and the variant exhibits a change in a biological activity. Allelic variants, for example in the context of a wildtype or predominant form of the receptor can be associated with a disease or condition. For example, amino acid changes occurring in the kinase domain of TEK receptor, such as at position 849, can be associated with vascular dysmorphogenesis due to increased activity of TEK. An exemplary TEK allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO: 309.

Exemplary Tie-2/TEK isoforms lack one or more domains or a part thereof compared to a cognate TEK such as set forth in SEQ ID NO:278. For example, exemplary TEK isoforms set forth in SEQ ID NO: 104, 105, 112, 131 and 133 lack a transmembrane domain and kinase domain. Tie-2/TEK isoforms can contain other domains of a Tie-2/TEK cognate receptor.. The exemplary TEK isoforms set forth as SEQ ID NO: 104 contains a laminin EGF – like domain between amino acids 219 – 268 and three fibronectin type III domains between amino acids 401 – 486, amino acids 500 – 580, and amino acids 593 - 678. The exemplary TEK isoforms set forth as SEQ ID NO: 105 contains a laminin EGF – like domain between amino acids 219 – 268 and three fibronectin type III domains between amino acids 444 – 529, amino acids 543 – 623, and amino acids 636 – 721. The exemplary TEK isoforms set forth as SEQ ID NO: 112 contains a laminin EGF – like domain between amino acids 196 – 245 and three fibronectin type III domains between amino acids 378 – 463, amino acids 477 – 557, and amino acids 570 – 655. The exemplary TEK isoform set forth as SEQ ID NO: 131 contains a laminin EGF-like domain between amino acids 219 – 268, but is missing the three fibronectin type III domains. The exemplary TEK isoform set forth as SEQ ID NO: 133 contains a laminin EGF-like domain between amino acids 219 – 268 and a portion of a fibronectin type III domain between amino acids 444 – 497.

TEK isoforms, including TEK isoforms herein, can include allelic variation in the TEK polypeptide. For example, a TEK isoform can include one or more amino acid differences present in an allelic variant. In one example, a TEK isoform

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includes one or more allelic variations as set forth in SEQ ID NO:309. An allelic variant can include one or more amino acid change in the fibronectin type III domain, such as at position 486 or 695. An allelic variant also can include one or more amino acid change, such as at position 346.

5           **9.       Tumor Necrosis Factor Receptors (TNFRs)**

          The TNF (tumor necrosis factor) ligand and receptor family regulate a variety of signal transduction pathways including those involved in cell differentiation, activation, and viability. TNFRs have a characteristic repeating extracellular cysteine-rich motif and a variable intracellular domain that differs between members  
10 of the TNFR family. The TNFR family of receptors includes, but is not limited to, TNFR1, TNFR2, TNFRp, the low-affinity nerve growth factor receptor, Fas antigen, CD40, CD27, CD30, 4-1BB, OX40, DR3, DR4, DR5, and herpesvirus entry mediator (HVEM). Ligands for TNFRs include TNF-  $\alpha$ , lymphotoxin, nerve growth factor, Fas ligand, CD40 ligand, CD27 ligand, CD30 ligand, 4-1BB ligand, OX40 ligand, APO3  
15 ligand, TRAIL and LIGHT. TNFRs include an extracellular domain, including a ligand binding domain, a transmembrane domain and an intracellular domain that participates in signal transduction. Additionally, TNFRs are typically trimeric proteins that trimerize at the cell surface. Trimerization is important for biological activity of TNFRs.

20           TNF plays a key role in inflammatory and infectious diseases. TNF binds two receptors, TNF-R1 and TNF-R2 that can transduce intracellular signals when expressed on the cell surface. TNFR1 is a major mediator of biological signaling involved in cell apoptosis, cytotoxicity, fibroblast proliferation, synthesis of prostaglandin E2 and resistance to Chlamydia. TNFR2 is involved in proliferation of  
25 thermocytes, TNF-dependent proliferative response to mononuclear cells, induction of GM-CSF secretion, inhibition of early hematopoiesis, and down-regulating activated T cells by inducing apoptosis. TNFR1 and TNFR2 also are produced as soluble forms by proteolytic cleavage (sTNFR). Increased levels of sTNFRs have been found in inflammatory and infectious diseases.

30           TNF/TNFRs are targets for many viruses. Viruses can bind to and sequester host cytokines, such as TNF, thus allowing the virus to escape the immune system.

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Many viruses encode proteins that mimic TNFR by binding TNF or that are viral homologs of TNFR. Viruses can upregulate TNF gene activity and/or expression, modulate TNF/TNFR effects, and bind to TNFR. TNFR isoforms, such as described herein, can be used to modulate TNFRs, including viral TNFR homologs and mimics.

- 5 Examples of viruses that interact with TNF/TNFRs and are targets for TNFR isoforms include, but are not limited to, DNA viruses including Myxoma virus, Vaccinia virus, Tanapox virus, Epstein-Barr virus, Herpes simplex virus, Cytomegalovirus, Herpesvirus saimiri, Hepatitis B virus, African swine fever virus and Parovirus, and RNA viruses including Human Immune deficiency virus (HIV), Hepatitis C virus, 10 Influenza virus, Respiratory syncytial virus, Measles virus, Vesicular stomatitis virus, Dengue virus and Ebola virus (see for example, Herbein *et al.* (2000) *Proc Soc Exp Biol Med.* 223(3):241-57). Exemplary TNFR isoforms include isoforms of TNFR1 such as set forth in SEQ ID NO: 95.

**a. TNFR1**

- 15 The TNFR1 polypeptide set forth as SEQ ID NO:280 (GenBank No. NP\_001056) is characterized by three TNFR c6 domains (between amino acids 44 – 81, amino acids 84 – 125, and amino acids 127 – 166), a transmembrane domain between amino acids 212 – 234, and a death domain between amino acids 357 – 441 within the cytoplasmic tail. The TNFR c6 domains are cysteine-rich domains at the 20 N-terminal region that can be subdivided into repeats containing six conserved cysteines, all of which are involved in intrachain disulfide bonds. Death domains are characteristic of the TNFR1 receptor family and are involved in initiating apoptosis and NF- $\kappa$ B and other signaling pathways upon ligand binding.

- TNFR1 polypeptides include allelic variants of TNFR1. In one example, an 25 allelic variant contains one or more amino acids changes compared to SEQ ID NO: 280. For example, one or more amino acid variations can occur in the c6 domains of TNFR2. An allelic variant can include single nucleotide polymorphisms (SNP) at position 75 (SNP No: 4149637) where, for example, P can be replaced by I, or at position 121 (SNP No. 4149584) where, for example, R can be replaced by Q. An 30 amino acid variation also can occur at position 305 where, for example, P can be



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replaced by T. An exemplary TNFR1 allelic variant containing one or more amino acid changes described above is set forth as SEQ ID NO: 311.

**b. TNFR2**

TNFR2 (GenBank No. NP\_001057 set forth as SEQ ID NO:281) is  
5 characterized by three TNFR c6 domains between amino acids 40 – 75, amino acids 78 – 118 and amino acids 120 – 161 and a transmembrane domain between amino acids 258 – 280. TNFR2 proteins include allelic variants of TNFR2. In one example, an allelic variant contains one or more amino acids changes compared to SEQ ID NO: 281. For example, one or more amino acid variations can occur in the  
10 transmembrane domain. An allelic variant can include single nucleotide polymorphisms at position 295 (SNP No: 5746032) where, for example, Q can be replaced by R. An amino acid variation also can occur at position 187 (SNP No: 5746025) where, for example, V can be replaced by M, or at position 196 (SNP No: 1061622) where, for example, M can be replaced by R, or at position 232 (SNP No:  
15 5746026) where, for example, E can be replaced by K, or at position 236 (SNP No: 5746027) where, for example, A can be replaced by T, or at position 264 (SNP No: 5746031) where, for example, L can be replaced by P. In one example, an allelic variant includes one or more amino acid changes compared to SEQ ID NO:281 and the variant exhibits a change in a biological activity. Allelic variants, for example in  
20 the context of a wildtype or predominant form of the receptor can be associated with a disease or condition. For example, amino acid changes occurring at position 196, for example, can be associated with autoimmune disease such as rheumatoid arthritis and acute graft-versus-host disease and diseases associated with polycystic ovary syndrome and hyperandrogenism. An exemplary TNFR2 allelic variant containing  
25 one or more amino acid changes described above is set forth as SEQ ID NO: 312.

Exemplary TNFR2 isoforms lack one or more domains or a part thereof compared to a cognate TNFR2 such as set forth in SEQ ID NO:281. The exemplary TNFR2 isoform set forth as SEQ ID NO:95 lacks a transmembrane domain. Additionally, this isoform is characterized by TNFR c6 domains between amino acids  
30 40 – 75 and amino acids 78 – 118 as well as a portion of a third c6 domain between amino acids 120 – 152.

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**G. Methods of Producing Nucleic Acid Encoding CSR Isoforms and Methods of Producing CSR isoform Polypeptides**

Exemplary methods for generating CSR isoform nucleic acid molecules and polypeptides are provided herein. Such methods include *in vitro* synthesis methods  
5 for nucleic acid molecules such as PCR, synthetic gene construction and *in vitro* ligation of isolated and/or synthesized nucleic acid fragments. CSR isoform nucleic acid molecules also can be isolated by cloning methods, including PCR of RNA and DNA isolated from cells and screening of nucleic acid molecule libraries by hybridization and/or expression screening methods.

10 CSR isoform polypeptides can be generated from CSR isoform nucleic acid molecules using *in vitro* and *in vivo* synthesis methods. CSR isoforms can be expressed in any organism suitable to produce the required amounts and forms of isoform needed for administration and treatment. Expression hosts include prokaryotic and eukaryotic organisms such as *E.coli*, yeast, plants, insect cells,  
15 mammalian cells, including human cell lines and transgenic animals. CSR isoforms also can be isolated from cells and organisms in which they are expressed, including cells and organisms in which isoforms are produced recombinantly and those in which isoforms are synthesized without recombinant means such as genomically-encoded isoforms produced by alternative splicing events.

20 **1. Synthetic genes and polypeptides**

CSR isoform nucleic acid molecules and polypeptides can be synthesized by methods known to one of skill in the art using synthetic gene synthesis. In such methods, a polypeptide of a CSR isoform is "back-translated" to generate one or more nucleic acid molecules encoding an isoform. The back-translated nucleic acid  
25 molecule is then synthesized as one or more DNA fragments such as by using automated DNA synthesis technology. The fragments are then operatively linked to form a nucleic acid molecule encoding an isoform. Nucleic acid molecules also can be joined with additional nucleic acid molecules such as vectors, regulatory sequences for regulating transcription and translation and other polypeptide-encoding nucleic  
30 acid molecules. Isoform-encoding nucleic acid molecules also can be joined with labels such as for tracking, including radiolabels, and fluorescent moieties.

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The process of backtranslation uses the genetic code to obtain a nucleotide gene sequence for any polypeptide of interest, such as a CSR isoform. The genetic code is degenerate, 64 codons specify 20 amino acids and 3 stop codons. Such degeneracy permits flexibility in nucleic acid design and generation, allowing for  
5 example restriction sites to be added to facilitate the linking of nucleic acid fragments and the placement of unique identifier sequences within each synthesized fragment. Degeneracy of the genetic code also allows the design of nucleic acid molecules to avoid unwanted nucleotide sequences, including unwanted restriction sites, splicing donor or acceptor sites, or other nucleotide sequences potentially detrimental to  
10 efficient translation. Additionally, organisms sometimes favor particular codon usage and/or a defined ratio of GC to AT nucleotides. Thus, degeneracy of the genetic code permits design of nucleic acid molecules tailored for expression in particular organisms or groups of organisms. Additionally, nucleic acid molecules can be designed for different levels of expression based on optimizing (or non-optimizing) of  
15 the sequences. Back-translation is performed by selecting codons that encode a polypeptide. Such processes can be performed manually using a table of the genetic code and a polypeptide. Alternatively, computer programs, including publicly available software can be used to generate back-translated nucleic acid sequences.

To synthesize a back-translated nucleic acid molecule, any method available  
20 in the art for nucleic acid synthesis can be used. For example, individual oligonucleotides corresponding to fragments of a CSR isoform-encoding sequence of nucleotides are synthesized by standard automated methods and mixed together in an annealing or hybridization reaction. Such oligonucleotides synthesized by such annealing result in the self-assembly of the gene from the oligonucleotides using  
25 overlapping single-stranded overhangs formed upon duplexing complementary sequences, generally about 100 nucleotides in length. Single nucleotide "nicks" in the duplex DNA are sealed using ligation, for example with bacteriophage T4 DNA ligase. Restriction endonuclease linker sequences can for example, then be used to insert the synthetic gene into any one of a variety of recombinant DNA vectors  
30 suitable for protein expression. In another, similar method, a series of overlapping oligonucleotides are prepared by chemical oligonucleotide synthesis methods.

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Annealing of these oligonucleotides results in a gapped DNA structure. DNA synthesis catalyzed by enzymes such as DNA polymerase I can be used to fill in these gaps, and ligation is used to seal any nicks in the duplex structure. PCR and/or other DNA amplification techniques can be applied to amplify the formed linear DNA duplex.

Additional nucleotide sequences can be joined to a CSR isoform-encoding nucleic acid molecule, including linker sequences containing restriction endonuclease sites for the purpose of cloning the synthetic gene into a vector, for example, a protein expression vector or a vector designed for the amplification of the core protein coding DNA sequences. Furthermore, additional nucleotide sequences specifying functional DNA elements can be operatively linked to an isoform-encoding nucleic acid molecule. Examples of such sequences include, but are not limited to, promoter sequences designed to facilitate intracellular protein expression, and secretion sequences designed to facilitate protein secretion. Additional nucleotide sequences such as sequences specifying protein binding regions also can be linked to isoform-encoding nucleic acid molecules. Such regions include, but are not limited to, sequences to facilitate uptake of an isoform into specific target cells, or otherwise enhance the pharmacokinetics of the synthetic gene.

CSR isoforms also can be synthesized using automated synthetic polypeptide synthesis. Cloned and/or *in silico*-generated polypeptides can be synthesized in fragments and then chemically linked. Alternatively, isoforms can be synthesized as a single polypeptide. Such polypeptides then can be used in the assays and treatment administrations described herein.

## **2. Methods of cloning and isolating CSR isoforms**

CSR isoforms can be cloned or isolated using any available methods known in the art for cloning and isolating nucleic acid molecules. Such methods include PCR amplification of nucleic acids and screening of libraries, including nucleic acid hybridization screening, antibody-based screening and activity-based screening.

Methods for amplification of nucleic acids can be used to isolate nucleic acid molecules encoding an isoform, including for example, polymerase chain reaction (PCR) methods. A nucleic acid containing material can be used as a starting material

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from which an isoform -encoding nucleic acid molecule can be isolated. For example, DNA and mRNA preparations, cell extracts, tissue extracts, fluid samples (e.g. blood, serum, saliva), samples from healthy and/or diseased subjects can be used in amplification methods. Nucleic acid libraries also can be used as a source of

5 starting material. Primers can be designed to amplify an isoform. For example, primers can be designed based on expressed sequences from which an isoform is generated. Primers can be designed based on back-translation of an isoform amino acid sequence. Nucleic acid molecules generated by amplification can be sequenced and confirmed to encode an isoform.

10 Nucleic acid molecules encoding isoforms also can be isolated using library screening. For example, a nucleic acid library representing expressed RNA transcripts as cDNA molecules can be screened by hybridization with nucleic acid molecules encoding CSR isoforms or portions thereof. For example, an intron sequence or portion thereof from a CSR gene can be used to screen for intron

15 retention containing molecules based on hybridization to homologous sequences. Expression library screening can be used to isolate nucleic acid molecules encoding a CSR isoform. For example, an expression library can be screened with antibodies that recognize a specific isoform or a portion of an isoform. Antibodies can be obtained and/or prepared which specifically bind to a CSR isoform or a region or

20 peptide contained in an isoform. Antibodies which specifically bind to an isoform can be used to screen an expression library containing nucleic acid molecules encoding an isoform, such as an intron fusion protein. Methods of preparing and isolating antibodies, including polyclonal and monoclonal antibodies and fragments therefrom are well known in the art. Methods of preparing and isolating recombinant and

25 synthetic antibodies also are well known in the art. For example, such antibodies can be constructed using solid phase peptide synthesis or can be produced recombinantly, using nucleotide and amino acid sequence information of the antigen binding sites of antibodies that specifically bind to a candidate polypeptide. Antibodies also can be obtained by screening combinatorial libraries containing variable heavy chains and

30 variable light chains, or antigen-binding portions thereof. Methods of preparing, isolating and using polyclonal, monoclonal and non-natural antibodies are reviewed,

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for example, in Kontermann and Dubel, eds. (2001) "Antibody Engineering" Springer Verlag; Howard and Bethell, eds. (2001) "Basic Methods in Antibody Production and Characterization" CRC Press; and O'Brien and Aitkin, eds. (2001) "Antibody Phage Display" Humana Press. Such antibodies also can be used to screen for the presence  
5 of an isoform polypeptide, for example, to detect the expression of a CSR isoform in a cell, tissue or extract.

### 3. Synthetic isoforms

A variety of synthetic forms of the isoforms are provided. Included among them are conjugates in which the isoform or intron-encoded portion thereof is linked  
10 directly or via linker to another agent, such as a targeting agent or to a molecule the present or provides the intron-encoded portion or isoform portion to the CSR so that an activity of the CSR is modulated. Other synthetic forms include chimeras in which the extracellular domain portion and C-terminal portion, such as an intron-encoded portion, are from different isoforms. Also provided are "peptidomimetic" isoforms in  
15 which one or more bonds in the peptide backbone is (are) replaced by a bioisotere or other bond such that the resulting polypeptide peptidomimetic has improved properties, such as resistance to proteases, compared to the unmodified form

#### a. Isoform conjugates

CSR isoforms also can be provided as conjugates between the isoform and  
20 another agent. The conjugate can be used to target to a receptor with which the isoform interacts and/or to another targeted receptor for delivery of isoform. Such conjugates include linkage of a CSR isoform to a targeted agent and/or targeting agent. Conjugates can be produced by any suitable method including chemical conjugation or by expression of fusion proteins in which, for example, DNA encoding  
25 a targeted agent or targeting agent, with or without a linker region, is operatively linked to DNA encoding an RTK isoform. Conjugates also can be produced by chemical coupling, typically through disulfide bonds between cysteine residues present in or added to the components, or through amide bonds or other suitable bonds. Ionic or other linkages also are contemplated.

30 Pharmaceutical compositions can be prepared that contain CSR isoform conjugates and treatment effected by administering a therapeutically effective amount

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of a conjugate, for example, in a physiologically acceptable excipient. CSR isoform conjugates also can be used in *in vivo* therapy methods such as by delivering a vector containing a nucleic acid encoding a CSR isoform conjugate as a fusion protein.

Conjugates can contain one or more CSR isoforms linked, either directly or  
5 via a linker, to one or more targeted agents: (CSR isoform)<sub>n</sub>, (L)<sub>q</sub>, and (targeted agent)<sub>m</sub> in which at least one CSR isoform is linked directly or via one or more linkers (L) to at least one targeted agent. Such conjugates also can be produced with any portion of a CSR isoform sufficient to bind to a target, such as a target cell type for treatment. Any suitable association among the elements of the conjugate and any  
10 number of elements where n, and m are integer greater than 1 and q is zero or any integer greater than 1, is contemplated as long as the resulting conjugates interacts with a targeted CSR or targeted cell type.

Examples of a targeted agent include drugs and other cytotoxic molecules such as toxins that act at or via the cell surface and those that act intracellularly.  
15 Examples of such moieties, include radionuclides, radioactive atoms that decay to deliver, *e.g.*, ionizing alpha particles or beta particles, or X-rays or gamma rays, that can be targeted when coupled to a CSR isoform. Other examples include chemotherapeutics that can be targeted by coupling with an isoform. For example, geldanamycin targets proteosomes. An isoform-geldanamycin molecule can be  
20 directed to intracellular proteosomes, degrading the targeted isoform and liberating geldanamycin at the proteosome. Other toxic molecules include toxins, such as ricin, saporin and natural products from conches or other members of phylum mollusca. Another example of a conjugate with a targeted agent is a CSR isoform coupled, for example as a protein fusion, with an antibody or antibody fragment. For example, an  
25 isoform can be coupled to an Fc fragment of an antibody that binds to a specific cell surface marker to induce killer T cell activity in neutrophils, natural killer cells, and macrophages. A variety of toxins are well known to those of skill in the art.

Conjugates can contain one or more CSR isoforms linked, either directly or via a linker, to one or more targeting agents: (CSR isoform)<sub>n</sub>, (L)<sub>q</sub>, and (targeting agent)<sub>m</sub> in which at least one CSR isoform is linked directly or via one or more  
30 linkers (L) to at least one targeting agent. Any suitable association among the

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elements of the conjugate and any number of elements where n, and m are integer greater than 1 and q is zero or any integer greater than 1, is contemplated as long as the resulting conjugates interacts with a target, such as a targeted cell type.

Targeting agents include any molecule that targets a CSR isoform to a target  
5 such as a particular tissue or cell type or organ. Examples of targeting agents include cell surface antigens, cell surface receptors, proteins, lipids and carbohydrate moieties on the cell surface or within the cell membrane, molecules processed on the cell surface, secreted and other extracellular molecules. Molecules useful as targeting agents include, but are not limited to, an organic compound; inorganic compound;  
10 metal complex; receptor; enzyme; antibody; protein; nucleic acid; peptide nucleic acid; DNA; RNA; polynucleotide; oligonucleotide; oligosaccharide; lipid; lipoprotein; amino acid; peptide; polypeptide; peptidomimetic; carbohydrate; cofactor; drug; prodrug; lectin; sugar; glycoprotein; biomolecule; macromolecule; biopolymer; polymer; and other such biological materials. Exemplary molecules useful as  
15 targeting agents include ligands for receptors, such as proteinaceous and small molecule ligands, and antibodies and binding proteins, such as antigen-binding proteins.

Alternatively, the CSR isoform, which specifically interacts with a particular receptor (or receptors) is the targeting agent and it is linked to targeted agent, such as  
20 a toxin, drug or nucleic acid molecule. The nucleic acid molecule can be transcribed and/or translated in the targeted cell or it can be regulatory nucleic acid molecule.

The CSR and be linked directly to the targeted (or targeting agent) or via a linker. Linkers include peptide and non-peptide linkers and can be selected for functionality, such as to relieve or decrease steric hindrance caused by proximity of a  
25 targeted agent or targeting agent to a CSR isoform and/or increase or alter other properties of the conjugate, such as the specificity, toxicity, solubility, serum stability and/or intracellular availability and/or to increase the flexibility of the linkage between a CSR isoform and a targeted agent or targeting agent. Examples of linkers and conjugation methods are known in the art (see, for example, WO 00/04926).  
30 CSRs also can be targeted using liposomes and other such moieties that direct delivery of encapsulated or entrapped molecules.



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**b. Chimeric and synthetic intron fusion polypeptides**

Also provided are chimeric and synthetic intron fusion polypeptides. These contain an intron from an intron fusion polypeptide operatively linked at the N-terminus to another polypeptide or other molecule such that the resulting molecule modulates the activity of a CSR, particularly an RTK, including any involved in pathways that participate in the inflammatory response, angiogenesis, neovascularization and/or cell proliferation. Included among these synthetic “polypeptides” are chimeric intron fusion polypeptides in which the N-terminus from the extracellular domain of a CSR is linked to the intron of an intron fusion protein, such as intron 8 of a herstatin (see, *e.g.*, SEQ ID Nos. 320-359). Exemplary herstatins are set forth in SEQ ID Nos. 320-359. Table 3A below identifies the sequences. Other herstatin variants include allelic variants, particularly those with variation in the extracellular domain portion.

15

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Table 3A

	Variant	Encoded Intron 8	SEQ ID NO (nucleotide)	SEQ ID NO (amino acid)
5	Herstatin prominent	AA: 341-419		320
	Intron 8 prominent- molecule in a bottle			321
	Herstatin variant (AA 342: Thr or Ser)	AA: 341-419		322
	Herstatin variant (AA 345: Leu or Pro)	AA: 341-419		323
	Herstatin variant (AA 346: Pro or Leu)	AA: 341-419		324
	Herstatin variant (AA 356: Leu or Gln)	AA 341-419		325
	Herstatin variant (AA 358: Met or Leu)	AA 341-419		326
10	Herstatin variant (AA 361: Gly, Asp, Ala, or Val)	AA 341-419		327
	Herstatin variant (AA 376: Leu or Ile)	AA 341-419		328
	Herstatin variant (AA 394: Pro or Arg)	AA 341-419		329
	Herstatin variant (AA 404: Pro or Leu)	AA 341-419		330
	Herstatin variant (AA 413: Asp or Asn)	AA 341-419		331
	Herstatin variant (AA 357: Arg or Cys)	AA 341-419		332
15	Herstatin variant (AA 371: Arg or Ile)	AA 341-419		333
				334
	Intron 8 variant (AA 2: Thr or Ser)			
	Intron 8 variant (AA 5: Leu or Pro)			335
	Intron 8 variant (AA 6: Pro or Leu)			336
	Intron 8 variant (AA 16: Leu or Gln)			337
	Intron 8 variant (AA 18: Met or Leu)			338
	Intron 8 variant (AA 21: Gly, Asp, Ala, or Val)			339
20				
	Intron 8 variant (AA 36: Leu or Ile)			340
	Intron 8 variant (AA 54: Pro or Arg)			341
	Intron 8 variant (AA 64: Pro or Leu)			342
	Intron 8 variant (AA 73: Asp or Asn)			343
	Intron 8 variant (AA 17: Arg or Cys)			344
	Intron 8 variant (AA 31: Arg or Ile)			345
	Intron 8 prominent- molecule in a bottle		346	
25				
	Intron 8 variant (nt 4: n= T)		347	
	Intron 8 variant (nt 14: n= C )		348	
	Intron 8 variant (nt: 17: n= T)		349	
	Intron 8 variant (nt 47= A)		350	
	Intron 8 variant (nt 54= A)		351	
	Intron 8 variant (nt 62: n= C,T, A)		352	
30				
	Intron 8 variant (nt 106= A)		353	
	Intron 8 variant (nt 161= G)		354	
	Intron 8 variant (nt 191: n= T)		355	
	Intron 8 variant (nt 217: C)		356	
	Intron 8 variant (nt 17: n= T and nt 217: n= C)		357	
	Intron 8 variant (nt 49: n=T)		358	
	Intron 8 variant (nt 92: n=T)		359	

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The N-terminus portion can be linked to a C-terminus (intron-encoded portion) of the synthetic intron fusion protein directly or via a linker, such as a polypeptide linker or a chemical linker. Linkage can be effected by recombinant expression of a fusion protein where there is no linker or where the linker is a polypeptide. Chemical synthesis also can be employed. When the linker is not a polypeptide, linkage can be effected chemically.

Any suitable linker can be selected so long as the resulting molecule interacts with a CSR and modulates, typically inhibits, its activity. Linkers can be selected to add a desirable property, such as to increase serum stability, solubility and/or intracellular concentration and to reduce steric hindrance caused by close proximity when one or more linkers is(are) inserted between the N-terminal portion and intron-encoded portion. The resulting molecule is designed or selected to retain the ability to modulate the activity of a CSR, particularly RTKs, including any involved in pathways that are involved in inflammatory responses, neovascularization, angiogenesis and cell proliferation.

Linkers include chemical linkers and peptide linkers, such as peptides that increase flexibility or solubility of the linked moieties, and chemical linkers. For example linkers can be inserted using heterobifunctional reagents, such as those described below, or, can be linked by linking DNA encoding polypeptide linker to the DNA encoding the N-terminal (and/or C-terminal portion) and expressing the resulting chimera. In addition, where no linker is present the N-terminus can be linked directly to the intron encoded portion. In some embodiments, the N-terminus portion can be replaced by non-peptidic moiety that provides sufficient steric hindrance and bulk to permit the intron-encoded portion to interact with and modulate the activity of a receptor. As noted above, the N-terminus also can be selected to target the intron-encoded portion to selected CSRs or a selected CSR.

Exemplary linkers include, but are not limited to, (Gly4Ser)<sub>n</sub>, (Ser4Gly)<sub>n</sub> and (AlaAlaProAla)<sub>n</sub> (see, SEQ ID NO: 319) in which n is 1 to 4, such as 1, 2, 3 or 4, such as:

(1) Gly4Ser with NcoI ends SEQ ID NO. 315  
CCATGGGCGG CGGCGGCTCT GCCATGG

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(2) (Gly4Ser)2 with NcoI ends SEQ ID NO. 316

CCATGGGCGG CGGCGGCTCT GGCGGCGGCG GCTCTGCCAT GG

(3) (Ser4Gly)4 with NcoI ends SEQ ID NO. 317

CCATGGCCTC GTCGTCGTCG GGCTCGTCGT CGTCGGGCTC

5 GTCGTCGTCG GGCTCGTCGT CGTCGGGCGC CATGG

(4) (Ser4Gly)2 with NcoI ends SEQ ID NO. 318

CCATGGCCTC GTCGTCGTCG GGCTCGTCGT CGTCGGGCGC CATGG

(5) (AlaAlaProAla)<sub>n</sub>, where n is 1 to 4, such as 2 or 3 (see, SEQ ID NO.:319)**c. Heterobifunctional cross-linking reagents**

10 Numerous heterobifunctional cross-linking reagents that are used to form covalent bonds between amino groups and thiol groups and to introduce thiol groups into proteins, are known to those of skill in this art (see, e.g., the PIERCE CATALOG, ImmunoTechnology Catalog & Handbook, 1992-1993, which describes the preparation of and use of such reagents and provides a commercial source for such

15 reagents; see, also, e.g., Cumber et al. (1992) Bioconjugate Chem. 3:397-401; Thorpe et al. (1987) Cancer Res. 47:5924-5931; Gordon et al. (1987) Proc. Natl. Acad. Sci. 84:308-312; Walden et al. (1986) J. Mol. Cell Immunol. 2:191-197; Carlsson et al. (1978) Biochem. J. 173: 723-737; Mahan et al. (1987) Anal. Biochem. 162:163-170; Wawryznaczak et al. (1992) Br. J. Cancer 66:361-366; Fattom et al. (1992) Infection

20 & Immun. 60:584-589). These reagents may be used to form covalent bonds between the N-terminal portion and C-terminus intron-encoded portion or between each of those portions and a linker. These reagents include, but are not limited to: N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP; disulfide linker); sulfosuccinimidyl 6-[3-(2-pyridyldithio)propionamido]hexanoate (sulfo-LC-SPDP);

25 succinimidyl-3-(2-pyridyldithio)propionamide (SPDP; hindered disulfate linker); succinimidyl 6-[3-(2-pyridyldithio)propionamido]hexanoate (LC-SPDP); sulfosuccinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (sulfo-SMCC); succinimidyl 3-(2-pyridyldithio)butyrate (SPDB; hindered disulfide bond linker); sulfosuccinimidyl 2-(7-azido-4-methylcoumarin-3-acetamide) ethyl-1,3'-

30 dithiopropionate (SAED); sulfo-succinimidyl 7-azido-4-methylcoumarin-3-acetate (SAMCA); sulfosuccinimidyl-6-[alpha-methyl-alpha-(2-pyridyldithio)toluamido]-

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hexanoate (sulfo-LC-SMPT); 1,4-di-[3'-(2'-pyridyldithio)propion-amido]butane (DPDPB); 4-succinimidylloxycarbonyl- $\alpha$ -methyl- $\alpha$ -(2-pyridylthio)toluene (SMPT, hindered disulfate linker); sulfosuccinimidyl-6-[ $\alpha$ -methyl- $\alpha$ -(2-pyrimidylthio)toluamido]hexanoate (sulfo-LC-SMPT); m-maleimidobenzoyl-N-hydroxy-succinimide ester (MBS); m-maleimidobenzoyl-N-hydroxysulfo-succinimide ester (sulfo-MBS); N-succinimidyl(4-iodoacetyl)aminobenzoate (SIAB; thioether linker); sulfosuccinimidyl-(4-iodoacetyl)amino benzoate (sulfo-SIAB); succinimidyl-4-(p-maleimido-phenyl)butyrate (SMPB); sulfosuccinimidyl-4-(p-maleimido-phenyl)butyrate (sulfo-SMPB); azidobenzoyl hydrazide (ABH). These linkers, for example, can be used in combination with peptide linkers, such as those that increase flexibility or solubility or that provide for or eliminate steric hindrance. Any other linkers known to those of skill in the art for linking a polypeptide molecule to another molecule can be employed. General properties are such that the resulting molecule is biocompatible (for administration to animals, including humans) and such that the resulting molecule modulates the activity of a CSR.

#### 4. Expression Systems

CSR isoforms, including natural and combinatorial intron fusion proteins, can be produced by any method known to those of skill in the art including *in vivo* and *in vitro* methods. CSR isoforms can be expressed in any organism suitable to produce the required amounts and forms of CSR isoforms needed for administration and treatment. Expression hosts include prokaryotic and eukaryotic organisms such as *E. coli*, yeast, plants, insect cells, mammalian cells, including human cell lines and transgenic animals. Expression hosts can differ in their protein production levels as well as the types of post-translational modifications that are present on the expressed proteins. The choice of expression host can be made based on these and other factors, such as regulatory and safety considerations, production costs and the need and methods for purification.

Many expression vectors are available and known to those of skill in the art and can be used for expression of CSR isoforms. The choice of expression vector will be influenced by the choice of host expression system. In general, expression vectors can include transcriptional promoters and optionally enhancers, translational signals,

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and transcriptional and translational termination signals. Expression vectors that are used for stable transformation typically have a selectable marker which allows selection and maintenance of the transformed cells. In some cases, an origin of replication can be used to amplify the copy number of the vector.

5           CSR isoforms also can be utilized or expressed as protein fusions. For example, an isoform fusion can be generated to add additional functionality to an isoform. Examples of isoform fusion proteins include, but are not limited to, fusions of a signal sequence, a tag such as for localization, *e.g.* a his<sub>6</sub> tag or a myc tag, or a tag for purification, for example, a GST fusion, and a sequence for directing protein  
10       secretion and/or membrane association.

**a.       Prokaryotic expression**

Prokaryotes, especially *E.coli*, provide a system for producing large amounts of proteins such as CSR isoforms. Transformation of *E.coli* is simple and rapid technique well known to those of skill in the art. Expression vectors for *E.coli* can  
15       contain inducible promoters, such promoters are useful for inducing high levels of protein expression and for expressing proteins that exhibit some toxicity to the host cells. Examples of inducible promoters include the lac promoter, the trp promoter, the hybrid tac promoter, the T7 and SP6 RNA promoters and the temperature regulated λPL promoter.

20           Isoforms can be expressed in the cytoplasmic environment of *E.coli*. The cytoplasm is a reducing environment and for some molecules, this can result in the formation of insoluble inclusion bodies. Reducing agents such as dithiothreitol and β-mercaptoethanol and denaturants, such as guanidine-HCl and urea can be used to resolubilize the proteins. An alternative approach is the expression of CSR isoforms  
25       in the periplasmic space of bacteria which provides an oxidizing environment and chaperonin-like and disulfide isomerases and can lead to the production of soluble protein. Typically, a leader sequence is fused to the protein to be expressed which directs the protein to the periplasm. The leader is then removed by signal peptidases inside the periplasm. Examples of periplasmic-targeting leader sequences include the  
30       pelB leader from the pectate lyase gene and the leader derived from the alkaline phosphatase gene. In some cases, periplasmic expression allows leakage of the

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expressed protein into the culture medium. The secretion of proteins allows quick and simple purification from the culture supernatant. Proteins that are not secreted can be obtained from the periplasm by osmotic lysis. Similar to cytoplasmic expression, in some cases proteins can become insoluble and denaturants and reducing agents can be used to facilitate solubilization and refolding. Temperature of induction and growth also can influence expression levels and solubility, typically temperatures between 25°C and 37°C are used. Typically, bacteria produce aglycosylated proteins. Thus, if proteins require glycosylation for function, glycosylation can be added *in vitro* after purification from host cells.

#### 10                   b.     Yeast

Yeasts such as *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Yarrowia lipolytica*, *Kluyveromyces lactis* and *Pichia pastoris* are well known yeast expression hosts that can be used for production of CSR isoforms. Yeast can be transformed with episomal replicating vectors or by stable chromosomal integration by homologous recombination. Typically, inducible promoters are used to regulate gene expression. Examples of such promoters include GAL1, GAL7 and GAL5 and metallothionein promoters, such as CUP1, AOX1 or other *Pichia* or other yeast promoter. Expression vectors often include a selectable marker such as LEU2, TRP1, HIS3 and URA3 for selection and maintenance of the transformed DNA. Proteins expressed in yeast are often soluble. Co-expression with chaperonins such as Bip and protein disulfide isomerase can improve expression levels and solubility. Additionally, proteins expressed in yeast can be directed for secretion using secretion signal peptide fusions such as the yeast mating type alpha-factor secretion signal from *Saccharomyces cerevisiae* and fusions with yeast cell surface proteins such as the Aga2p mating adhesion receptor or the *Arxula adenivorans* glucoamylase. A protease cleavage site such as for the Kex-2 protease, can be engineered to remove the fused sequences from the expressed polypeptides as they exit the secretion pathway. Yeast also is capable of glycosylation at Asn-X-Ser/Thr motifs.

#### 25                   c.     Insect cells

30                   Insect cells, particularly using baculovirus expression, are useful for expressing polypeptides such as CSR isoforms. Insect cells express high levels of

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protein and are capable of most of the post-translational modifications used by higher eukaryotes. Baculovirus have a restrictive host range which improves the safety and reduces regulatory concerns of eukaryotic expression. Typical expression vectors use a promoter for high level expression such as the polyhedrin promoter of baculovirus.

5 Commonly used baculovirus systems include the baculoviruses such as *Autographa californica* nuclear polyhedrosis virus (AcNPV), and the *bombyx mori* nuclear polyhedrosis virus (BmNPV) and an insect cell line such as Sf9 derived from *Spodoptera frugiperda*, *Pseudaletia unipuncta* (A7S) and *Danaus plexippus* (DpN1). For high-level expression, the nucleotide sequence of the molecule to be expressed is

10 fused immediately downstream of the polyhedrin initiation codon of the virus. Mammalian secretion signals are accurately processed in insect cells and can be used to secrete the expressed protein into the culture medium. In addition, the cell lines *Pseudaletia unipuncta* (A7S) and *Danaus plexippus* (DpN1) produce proteins with glycosylation patterns similar to mammalian cell systems.

15 An alternative expression system in insect cells is the use of stably transformed cells. Cell lines such as the Schnieder 2 (S2) and Kc cells (*Drosophila melanogaster*) and C7 cells (*Aedes albopictus*) can be used for expression. The *Drosophila* metallothionein promoter can be used to induce high levels of expression in the presence of heavy metal induction with cadmium or copper. Expression vectors

20 are typically maintained by the use of selectable markers such as neomycin and hygromycin.

#### **d. Mammalian cells**

Mammalian expression systems can be used to express CSR isoforms. Expression constructs can be transferred to mammalian cells by viral infection such as

25 adenovirus or by direct DNA transfer such as liposomes, calcium phosphate, DEAE-dextran and by physical means such as electroporation and microinjection. Expression vectors for mammalian cells typically include an mRNA cap site, a TATA box, a translational initiation sequence (Kozak consensus sequence) and polyadenylation elements. Such vectors often include transcriptional promoter-

30 enhancers for high-level expression, for example the SV40 promoter-enhancer, the human cytomegalovirus (CMV) promoter and the long terminal repeat of Rous



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sarcoma virus (RSV). These promoter-enhancers are active in many cell types. Tissue and cell-type promoters and enhancer regions also can be used for expression. Exemplary promoter/enhancer regions include, but are not limited to, those from genes such as elastase I, insulin, immunoglobulin, mouse mammary tumor virus, albumin, alpha fetoprotein, alpha 1 antitrypsin, beta globin, myelin basic protein, myosin light chain 2, and gonadotropic releasing hormone gene control. Selectable markers can be used to select for and maintain cells with the expression construct. Examples of selectable marker genes include, but are not limited to, hygromycin B phosphotransferase, adenosine deaminase, xanthine-guanine phosphoribosyl transferase, aminoglycoside phosphotransferase, dihydrofolate reductase and thymidine kinase. Fusion with cell surface signaling molecules such as TCR- $\zeta$  and Fc $\epsilon$ RI- $\gamma$  can direct expression of the proteins in an active state on the cell surface.

Many cell lines are available for mammalian expression including mouse, rat human, monkey, chicken and hamster cells. Exemplary cell lines include but are not limited to CHO, Balb/3T3, HeLa, MT2, mouse NS0 (nonsecreting) and other myeloma cell lines, hybridoma and heterohybridoma cell lines, lymphocytes, fibroblasts, Sp2/0, COS, NIH3T3, HEK293, 293S, 2B8, and HKB cells. Cell lines also are available that are adapted to serum-free media which facilitates purification of secreted proteins from the cell culture media. One such example is the serum free EBNA-1 cell line (Pham *et al.*, (2003) *Biotechnol. Bioeng.* 84:332-42.)

#### e. Plants

Transgenic plant cells and plants can be used to express CSR isoforms. Expression constructs are typically transferred to plants using direct DNA transfer such as microprojectile bombardment and PEG-mediated transfer into protoplasts, and with agrobacterium-mediated transformation. Expression vectors can include promoter and enhancer sequences, transcriptional termination elements and translational control elements. Expression vectors and transformation techniques are usually divided between dicot hosts, such as *Arabidopsis* and tobacco, and monocot hosts, such as corn and rice. Examples of plant promoters used for expression include the cauliflower mosaic virus promoter, the nopaline synthase promoter, the ribose biphosphate carboxylase promoter and the ubiquitin and UBQ3 promoters.

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Selectable markers such as hygromycin, phosphomannose isomerase and neomycin phosphotransferase are often used to facilitate selection and maintenance of transformed cells. Transformed plant cells can be maintained in culture as cells, aggregates (callus tissue) or regenerated into whole plants. Transgenic plant cells also  
5 can include algae engineered to produce CSR isoforms (see for example, Mayfield *et al.* (2003) *PNAS* 100:438-442). Because plants have different glycosylation patterns than mammalian cells, this can influence the choice of CSR isoforms produced in these hosts.

#### 5. Engineered CSR isoforms

10 CSR isoforms can be designed and produced with one or more modified properties. These properties include but are not limited to increased protein stability, such as an increased protein half-life, increased thermal tolerance and/or resistance to one or more proteases. For example, a CSR isoform can be modified to increase protein stability *in vitro* and/or *in vivo*. *In vivo* stability can include protein stability  
15 under particular administration conditions such as stability in blood, saliva, and/or digestive fluids.

##### a. Modified proteins

CSR isoforms can be modified using any methods known in the art for modification of proteins. Such methods include site-directed and random  
20 mutagenesis. Non-natural amino acids and/or non-natural covalent bonds between amino acids of the polypeptide can be introduced into a CSR isoform to increase protein stability. In such modified CSR isoforms, the biological function of the isoform can remain unchanged compared to the unmodified isoform. Assays such as the assays for biological function provided herein and known in the art can be used to  
25 assess the biological function of a modified CSR isoform

##### b. Peptidomimetic isoforms.

Also provided are "peptidomimetic" isoforms in which one or more bonds in the peptide backbone (or other bond(s)) is (are) replaced by a bioisotere or other bond such that the resulting polypeptide peptidomimetic has improved properties, such as  
30 resistance to proteases, compared to the unmodified form.

#### H. Assays to assess or monitor isoform activities or affects on CSR Activities

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CSR isoforms can exhibit alterations in structure or in one or more activities compared to a full-length, wildtype or predominant form of a receptor. In addition, the CSR isoforms can alter (modulate) the activity of a CSR. All such isoforms are candidate therapeutics.

5           Where the isoforms exhibit a difference in an activity, *in vitro* and *in vivo* assays can be used to monitor or screen CSR isoforms. *In vitro* and *in vivo* assays also can be used to screen CSR isoforms to identify or select those that modulate the activity of a particular receptor or pathway. Such assays are well known to those of skill in the art. One of skill in the art can test a particular isoform for interaction with  
10 a CSR or a CSR ligand and/or test to assess any change in activity compared to a CSR. Some are exemplified herein.

Exemplary *in vitro* and *in vivo* assays are provided herein for comparison of an activity of an RTK isoform to an activity of a wildtype or predominant form of an RTK. Many of the assays are applicable to other CSRs and CSR isoforms. In  
15 addition, numerous assays, such as assays for kinase activities and cell proliferation activities of CSRs are known to one of skill in the art. Assays for activities of RTK isoforms and RTKs include, but are not limited to, kinase assays, homodimerization and heterodimerization assays, protein:protein interaction assays, structural assays, cell signaling assays and *in vivo* phenotyping assays. Assays also include employing  
20 animal models, including disease models in which an activity can be observed and/or measured or otherwise assessed. Dose response curves of a CSR isoform in such assays can be used to assess modulation of biological activities and as well as to determine therapeutically effective amounts of a CSR isoform for administration. Assays for RTK isoforms and RTKs include, but are not limited to, kinase assays,  
25 homodimerization and heterodimerization assays, protein:protein interaction assays, structural assays, cell signaling assays and *in vivo* phenotyping assays. Assays for TNFRs include, but are not limited, trimerization assays, localization assays such as membrane localization assays, protein:protein interaction assays, structural assays, cell signaling assays and *in vivo* phenotyping assays. Exemplary assays are described  
30 below.

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### 1. Kinase assays

Kinase activity can be detected and/or measured directly and indirectly. For example, antibodies against phosphotyrosine can be used to detect phosphorylation of an RTK, RTK isoform, an RTK:RTK isoform complex and phosphorylation of other proteins and signaling molecules. For example, activation of tyrosine kinase activity of an RTK can be measured in the presence of a ligand for an RTK.

Transphosphorylation can be detected by anti-phosphotyrosine antibodies.

Transphosphorylation can be measured and/or detected in the presence and absence of an RTK isoform, thus measuring the ability of an RTK isoform to modulate the transphosphorylation of an RTK. Briefly, cells expressing an RTK isoform or that have been exposed to an RTK isoform, are treated with ligand. Cells are lysed and protein extracts (whole cell extracts or fractionated extracts) are loaded onto a polyacrylamide gel, separated by electrophoresis and transferred to membrane, such as used for western blotting. Immunoprecipitation with anti-RTK antibodies also can be used to fractionate and isolate RTK proteins before performing gel electrophoresis and western blotting. The membranes can be probed with anti-phosphotyrosine antibodies to detect phosphorylation as well as probed with anti-RTK antibodies to detect total RTK protein. Control cells, such as cells not expressing RTK isoform and cells not exposed to ligand can be subjected to the same procedures for comparison.

Tyrosine phosphorylation also can be measured directly, such as by mass spectroscopy. For example, the effect of an RTK isoform on the phosphorylation state of an RTK can be measured, such as by treating intact cells with various concentrations of an RTK isoform and measuring the effect on activation of an RTK. The RTK can be isolated by immunoprecipitation and trypsinized to produce peptide fragments for analysis by mass spectroscopy. Peptide mass spectroscopy is a well-established method for quantitatively determining the extent of tyrosine phosphorylation for proteins; phosphorylation of tyrosine increases the mass of the peptide ion containing the phosphotyrosine, and this peptide is readily separated from the non-phosphorylated peptide by mass spectroscopy.

For example, tyrosine-1139 and tyrosine-1248 are known to be autophosphorylated in the ErbB2 RTK. Trypsinized peptides can be empirically

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determined or predicted based on polypeptide, for example by using ExPASy-PeptideMass program. The extent of phosphorylation of tyrosine-1139 and tyrosine-1248 can be determined from the mass spectroscopy data of peptides containing these tyrosines. Such assays can be used to assess the extent of auto-phosphorylation of an RTK isoform and the ability of an RTK isoform to transphosphorylate an RTK.

## **2. Complexation**

Complexation, such as dimerization of RTKs and RTK isoforms and trimerization of TNFRs and TNFR isoforms, can be detected and/or measured. For example, isolated polypeptides can be mixed together, subjected to gel electrophoresis and western blotting. CSRs and/or CSR isoforms also can be added to cells and cell extracts, such as whole cell or fractionated extracts, and can be subjected to gel electrophoresis and western blotting. Antibodies recognizing the polypeptides can be used to detect the presence of monomers, dimers and other complexed forms. Alternatively, labeled CSRs and/or labeled CSR isoforms can be detected in the assays.

For example, such assays can be used to compare homodimerization of an RTK or heterodimerization of two or more RTKs in the presence and absence of an RTK isoform. Assays also can be performed to assess homodimerization of an RTK isoform and/or its ability to heterodimerize with an RTK. For example an ErbB2 RTK isoform can be assessed for its ability to heterodimerize with ErbB2, ErbB3 and ErbB4. Additionally, an ErbB2 RTK isoform can be assessed for its ability to modulate the ability of ErbB2 to homodimerize with itself.

## **3. Ligand binding**

Generally, CSRs bind to one or more ligands. Ligand binding modulates the activity of the receptor and thus modulates, for example, signaling within a signal transduction pathway. Ligand binding of a CSR isoform and ligand binding of a CSR in the presence of a CSR isoform can be measured. For example, labeled ligand such as radiolabeled ligand can be added to purified or partially purified CSR in the presence and absence (control) of a CSR isoform. Immunoprecipitation and measurement of radioactivity can be used to quantify the amount of ligand bound to a CSR in the presence and absence of a CSR isoform. A CSR isoform also can be

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assessed for ligand binding such as by incubating a CSR isoform with labeled ligand and determining the amount of labeled ligand bound by a CSR isoform, for example, compared to an amount bound by a wildtype or predominant form of a corresponding CSR.

5           **4. Cell Proliferation assays**

A number of RTKs, for example VEGFR, are involved in cell proliferation. Effects of an RTK isoform on cell proliferation can be measured. For example, ligand can be added to cells expressing an RTK. An RTK isoform can be added to such cells before, concurrently or after ligand addition and effects on cell proliferation  
10 measured. Alternatively an RTK isoform can be expressed in such cell models, for example using an adenovirus vector. For example, a VEGFR isoform is added to endothelial cells expressing VEGFR. Following isoform addition, VEGF ligand is added and the cells are incubated at standard growth temperature (*e.g.* 37°C) for several days. Cells are trypsinized, stained with trypan blue and viable cells are  
15 counted. Cells not exposed to VEGFR isoform and/or ligand are used as controls for comparison. Other suitable controls can be employed.

**5. Cell disease model assays**

Cells from a disease or condition or that can be modulated to mimic a disease or condition can be used to measure/and or detect the effect of an CSR isoform.  
20 Numerous animal and *in vitro* disease models are known to those of skill in the art. For example, a CSR isoform is added or expressed in cells and a phenotype is measured or detected in comparison to cells not exposed to or not expressing a CSR isoform. Such assays can be used to measure effects including effects on cell proliferation, metastasis, inflammation, angiogenesis, pathogen infection and bone  
25 resorption.

For example, effects of a MET isoform can be measured using such assays. A liver cell model such as HepG2 liver cells can be used to monitor the infectivity of malaria in culture by sporozoites. An RTK isoform such as a MET isoform can be added to the cells and/or expressed in the cells. Infection of such cells with malaria  
30 sporozoites is then measured, such as by staining and counting the EEFs (exoerythrocytic forms) of the sporozoite that are produced as a result of infection

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Carrolo *et al.* (2003) *Nat Med* 9(11):1363-1369. Effects of an RTK isoform can be assessed by comparing results to cells not exposed or expressing an RTK isoform and/or uninfected cells.

Effects of a CSR isoform also can be measured in angiogenesis. For example, tubule formation by endothelial cells such as human umbilical vein endothelial cells (HUVEC) *in vitro* can be used as an assay to measure angiogenesis and effects on angiogenesis. Addition of varying amounts of a CSR isoform to an *in vitro* angiogenesis assay is a method suitable for screening the effectiveness of a CSR isoform as a modulator of angiogenesis.

Bone resorption can be measured in cell culture to measure effectiveness of an RTK-isoform, such as by using osteoclast cultures. Osteoclasts are highly differentiated cells of hematopoietic origin that resorb bone in the organism, and are able to resorb bone from bone slices *in vitro*. Methods for cell culture of osteoclasts and quantitative techniques for measuring bone resorption in osteoclast cell culture have been described in the art. For example, mononuclear cells can be isolated from human peripheral blood and cultured. Addition and/or expression of a CSR isoform can be used to assess effects on osteoclast formation such as by measuring multinucleated cells positive for tartrate-resistant acid phosphatase and resorbed area and collagen fragments released from bone slices. Dose response curves can be used to determine therapeutically effective amounts of a CSR isoform necessary to modulate bone resorption.

## 6. Animal models

Animal models can be used to assess the effect of a CSR isoform. In one example, animal models of disease can be studied to determine if introduction of a CSR isoform affects the disease. For example, CSR isoform effects on tumor formation including cancer cell proliferation, migration and invasiveness can be measured. In one such assay, cancer cells such as ovarian cancer cells are infected with an adenovirus expressing a CSR isoform. After a culturing period *in vitro*, cells are trypsinized, suspended in a suitable buffer and injected into mice (e.g., subcutaneously into flanks and shoulders of model mice such as Balb/c nude mice). Tumor growth is monitored over time. Control cells, not expressing a CSR isoform,

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can be injected into mice for comparison. Similar assays can be performed with other cell types and animal models, for example, NIH3T3 cells, murine lung carcinoma (LLC) cells, primary Pancreatic Adenocarcinoma (PANC-1) cells, TAKA-1 pancreatic ductal cells, and C57BL/6 mice and SCID mice. In a further example, effects of CSR isoforms on ocular disorders can be assessed using assays such as a corneal micropocket assay. Briefly, mice receive cells expressing a CSR isoform (or control) by injection 2-3 days before the assay. Subsequently, the mice are anesthetized, and pellets of a ligand are implanted into the corneal micropocket of the eyes. Neovascularization is then measured, for example, 5 days following implantation. The effect of a CSR isoform on angiogenesis and eye phenotype compared to a control is then assessed. In an additional example, effects of a CSR isoform in a model of collagen type II-induced arthritis (CIA) can be assessed by intraperitoneal injection of SCID mice with splenocytes from DBA/1 mice that have been transduced with a retroviral vector containing the cDNA of a CSR isoform or unmodified splenocytes. Mice that receive unmodified splenocytes develop arthritis within 11-13 days and can be used as a reference control to determine effects of CSR isoform-expressing splenocytes on the development of arthritis as assessed, for example, by clinical, histological, or immunological (i.e. antibody levels) parameters of arthritis.

Effects of CSR isoforms on animal models of disease additionally can be assessed by the administration of purified or recombinant forms of a CSR isoform. For example, wound healing can be assessed in a model of impaired wound healing utilizing genetically diabetic db+/db+ mice whereby full-thickness excisional wounds are created on the backs of diabetic mice. Following treatment with a CSR isoform, either topically or systemically, wound healing can be assessed by analyzing for wound closure, inflammatory cell infiltration at the site of the wound, and expression of inflammatory cytokines. The effects of CSR isoforms on wound healing can be assessed over time and effects can be compared to mice that receive a control treatment, for example a vehicle only control. In a further example, a recombinant CSR isoform can be administered in a model of pulmonary fibrosis induced by bleomycin or silica to determine if lung fibrosis is reduced as assessed, for example,



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by analysis of histological sections for lung damage and by assaying for effects on bleomycin/silica induced increases of lung hydroxyproline content.

Animals deficient in a CSR isoform also can be used to monitor the biological activity of a CSR isoform. For example an isoform-specific disruption can be made by creating a targeted construct whereby upstream from an IRES-LacZ cassette, translational stop codons are introduced within the appropriate reading frame to ensure that the receptor protein terminates early. Alternatively, a LoxP/Cre recombination strategy can be used. Following confirmation of the targeted disruption, the consequences of a deficiency in a CSR isoform can be established by analyzing the phenotype of the deficient mice compared to wildtype mice including the development of various organs such as, for example, lung, limbs, eyelids, anterior pituitary gland, and pancreas. In addition, by histology or isolation of specific cell populations, other parameters, such as apoptosis or cell proliferation, can be assessed to determine if there is a difference between animals or isolated cells lacking the CSR isoform compared to wildtype CSR. Components of signaling cascades and expression of downstream genes also can be assessed to determine if the absence of a CSR isoform affects receptor signaling and gene expression.

**I. Preparation, Formulation and Administration of CSR isoforms and CSR isoform compositions**

CSR isoforms and CSR isoform compositions, including RTK and TNFR isoforms and RTK and TNFR isoform compositions, can be formulated for administration by any route known to those of skill in the art including intramuscular, intravenous, intradermal, intraperitoneal injection, subcutaneous, epidural, nasal oral, rectal, topical, inhalational, buccal (*e.g.*, sublingual), and transdermal administration or any route. CSR isoforms can be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and can be administered with other biologically active agents, either sequentially, intermittently or in the same composition. Administration can be local, topical or systemic depending upon the locus of treatment. Local administration to an area in need of treatment can be achieved by, for example, but not limited to, local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by

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means of a catheter, by means of a suppository, or by means of an implant.

Administration also can include controlled release systems including controlled release formulations and device controlled release, such as by means of a pump. The most suitable route in any given case will depend on the nature and severity of the disease or condition being treated and on the nature of the particular composition which is used.

Various delivery systems are known and can be used to administer CSR isoforms, such as but not limited to, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor mediated endocytosis, and delivery of nucleic acid molecules encoding CSR isoforms such as retrovirus delivery systems.

Pharmaceutical compositions containing CSR isoforms can be prepared. Generally, pharmaceutically acceptable compositions are prepared in view of approvals for a regulatory agency or other prepared in accordance with generally recognized pharmacopeia for use in animals and in humans. Pharmaceutical compositions can include carriers such as a diluent, adjuvant, excipient, or vehicle with which an isoform is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, and sesame oil. Water is a typical carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions also can be employed as liquid carriers, particularly for injectable solutions. Compositions can contain along with an active ingredient: a diluent such as lactose, sucrose, dicalcium phosphate, or carboxymethylcellulose; a lubricant, such as magnesium stearate, calcium stearate and talc; and a binder such as starch, natural gums, such as gum acaciagelatin, glucose, molasses, polyvinylpyrrolidone, celluloses and derivatives thereof, povidone, crospovidones and other such binders known to those of skill in the art. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, and ethanol. A composition, if desired, also can contain minor amounts of wetting or emulsifying agents, or pH

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buffering agents, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, and sustained release formulations. A composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and other such agents. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. Such compositions will contain a therapeutically effective amount of the compound, generally in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

Formulations are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable derivatives thereof. Pharmaceutically therapeutically active compounds and derivatives thereof are typically formulated and administered in unit dosage forms or multiple dosage forms. Each unit dose contains a predetermined quantity of therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit dose forms include ampoules and syringes and individually packaged tablets or capsules. Unit dose forms can be administered in fractions or multiples thereof. A multiple dose form is a plurality of identical unit dosage forms packaged in a single container to be administered in segregated unit dose form. Examples of multiple dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit doses that are not segregated in packaging.

Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non-toxic carrier can be prepared. For oral administration, pharmaceutical compositions can take the form of, for

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example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, pregelatinized maize starch, polyvinyl pyrrolidone or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (*e.g.*,  
5 magnesium stearate, talc or silica); disintegrants (*e.g.*, potato starch or sodium starch glycolate); or wetting agents (*e.g.*, sodium lauryl sulphate). The tablets can be coated by methods well-known in the art.

Pharmaceutical preparation also can be in liquid form, for example, solutions, syrups or suspensions, or can be presented as a drug product for reconstitution with  
10 water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters, or fractionated vegetable oils); and preservatives (*e.g.*, methyl or  
15 propyl-p-hydroxybenzoates or sorbic acid).

Formulations suitable for rectal administration can be provided as unit dose suppositories. These can be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

20 Formulations suitable for topical application to the skin or to the eye include ointments, creams, lotions, pastes, gels, sprays, aerosols and oils. Exemplary carriers include Vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The topical formulations also can contain 0.05 to 15, 20, 25 percent by weight of thickeners selected from among hydroxypropyl methyl cellulose, methyl  
25 cellulose, polyvinylpyrrolidone, polyvinyl alcohol, poly (alkylene glycols), poly/hydroxyalkyl, (meth)acrylates or poly(meth)acrylamides. A topical formulation is often applied by instillation or as an ointment into the conjunctival sac. It also can be used for irrigation or lubrication of the eye, facial sinuses, and external auditory meatus. It also can be injected into the anterior eye chamber and other places. A  
30 topical formulation in the liquid state can be also present in a hydrophilic three-

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dimensional polymer matrix in the form of a strip or contact lens, from which the active components are released.

For administration by inhalation, the compounds for use herein can be delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin, for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Formulations suitable for buccal (sublingual) administration include, for example, lozenges containing the active compound in a flavored base, usually sucrose and acacia or tragacanth; and pastilles containing the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Pharmaceutical compositions of CSR isoforms can be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions can be suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water or other solvents, before use.

Formulations suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound as an optionally buffered aqueous solution of, for example, 0.1 to 0.2M concentration with respect to the active compound. Formulations suitable for transdermal administration also can be delivered by iontophoresis (see, e.g., *Pharmaceutical Research* 3(6), 318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound.

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Pharmaceutical compositions also can be administered by controlled release means and/or delivery devices (see, *e.g.*, in U.S. Patent Nos. 3,536,809; 3,598,123; 3,630,200; 3,845,770; 3,847,770; 3,916,899; 4,008,719; 4,687,610; 4,769,027; 5,059,595; 5,073,543; 5,120,548; 5,354,566; 5,591,767; 5,639,476; 5,674,533 and  
5 5,733,566).

In certain embodiments, liposomes and/or nanoparticles may also be employed with CSR isoform administration. Liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs). MLVs generally have  
10 diameters of from 25 nm to 4  $\mu$ m. Sonication of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters in the range of 200 to 500  $\text{\AA}$ ., containing an aqueous solution in the core.

Phospholipids can form a variety of structures other than liposomes when dispersed in water, depending on the molar ratio of lipid to water. At low ratios, the  
15 liposomes form. Physical characteristics of liposomes depend on pH, ionic strength and the presence of divalent cations. Liposomes can show low permeability to ionic and polar substances, but at elevated temperatures undergo a phase transition which markedly alters their permeability. The phase transition involves a change from a closely packed, ordered structure, known as the gel state, to a loosely packed, less-  
20 ordered structure, known as the fluid state. This occurs at a characteristic phase-transition temperature and results in an increase in permeability to ions, sugars and drugs.

Liposomes interact with cells via different mechanisms: Endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and  
25 neutrophils; adsorption to the cell surface, either by nonspecific weak hydrophobic or electrostatic forces, or by specific interactions with cell-surface components; fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal contents into the cytoplasm; and by transfer of liposomal lipids to cellular or subcellular membranes, or  
30 vice versa, without any association of the liposome contents. Varying the liposome formulation can alter which mechanism is operative, although more than one may

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operate at the same time. Nanocapsules can generally entrap compounds in a stable and reproducible way. To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1  $\mu\text{m}$ ) should be designed using polymers able to be degraded in vivo. Biodegradable polyalkyl-cyanoacrylate  
5 nanoparticles that meet these requirements are contemplated for use herein, and such particles can be easily made.

Administration methods can be employed to decrease the exposure of CSR isoforms to degradative processes, such as proteolytic degradation and immunological intervention via antigenic and immunogenic responses. Examples of such methods  
10 include local administration at the site of treatment. Pegylation of therapeutics has been reported to increase resistance to proteolysis; increase plasma half-life, and decrease antigenicity and immunogenicity. Examples of pegylation methodologies are known in the art (see for example, Lu and Felix, *Int. J. Peptide Protein Res.*, 43: 127-138, 1994; Lu and Felix, *Peptide Res.*, 6: 142-6, 1993; Felix *et al.*, *Int. J. Peptide*  
15 *Res.*, 46 : 253-64, 1995; Benhar *et al.*, *J. Biol. Chem.*, 269: 13398-404, 1994; Brumeanu *et al.*, *J Immunol.*, 154: 3088-95, 1995; see also, Caliceti *et al.* (2003) *Adv. Drug Deliv. Rev.* 55(10):1261-77 and Molineux (2003) *Pharmacotherapy* 23 (8 Pt 2):3S-8S). Pegylation also can be used in the delivery of nucleic acid molecules in vivo. For example, pegylation of adenovirus can increase stability and gene transfer  
20 (see, e.g., Cheng *et al.* (2003) *Pharm. Res.* 20(9): 1444-51).

Desirable blood levels can be maintained by a continuous infusion of the active agent as ascertained by plasma levels. It should be noted that the attending physician would know how to and when to terminate, interrupt or adjust therapy to lower dosage due to toxicity, or bone marrow, liver or kidney dysfunctions.  
25 Conversely, the attending physician would also know how to and when to adjust treatment to higher levels if the clinical response is not adequate (precluding toxic side effects). administered, for example, by oral, pulmonary, parental (intramuscular, intraperitoneal, intravenous (IV) or subcutaneous injection), inhalation (via a fine powder formulation), transdermal, nasal, vaginal, rectal, or sublingual routes of  
30 administration and can be formulated in dosage forms appropriate for each route of

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administration (see, *e.g.*, International PCT application Nos. WO 93/25221 and WO 94/17784; and European Patent Application 613,683).

5 A CSR isoform is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. Therapeutically effective concentration can be determined empirically by testing the compounds in known *in vitro* and *in vivo* systems, such as the assays provided herein.

10 The concentration a CSR isoform in the composition will depend on absorption, inactivation and excretion rates of the complex, the physicochemical characteristics of the complex, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. The amount of a CSR isoform to be administered for the treatment of a disease or condition, for example cancer, autoimmune disease and infection can be determined by standard clinical techniques. In addition, *in vitro* assays and animal models can be employed to help identify  
15 optimal dosage ranges. The precise dosage, which can be determined empirically, can depend on the route of administration and the seriousness of the disease. Suitable dosage ranges for administration can range from about 0.01 pg/kg body weight to 1 mg/kg body weight and more typically 0.05 mg/kg to 200 mg/kg CSR isoform: patient weight.

20 A CSR isoform can be administered at once, or can be divided into a number of smaller doses to be administered at intervals of time. CSR isoforms can be administered in one or more doses over the course of a treatment time for example over several hours, days, weeks, or months. In some cases, continuous administration is useful. It is understood that the precise dosage and duration of treatment is a  
25 function of the disease being treated and can be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values also can vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and  
30 the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein



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are exemplary only and are not intended to limit the scope or use of compositions and combinations containing them.

**J. *In Vivo* Expression of CSR isoforms and Gene therapy**

CSR isoforms can be delivered to cells and tissues by expression of nucleic acid molecules. CSR isoforms can be administered as nucleic acid molecules  
5 encoding a CSR isoform, including *ex vivo* techniques and direct *in vivo* expression.

**1. Delivery of nucleic acids**

Nucleic acids can be delivered to cells and tissues by any method known to those of skill in the art.

**10 a. Vectors – episomal and integrating**

Methods for administering CSR isoforms by expression of encoding nucleic acid molecules include administration of recombinant vectors. The vector can be designed to remain episomal, such as by inclusion of an origin of replication or can be designed to integrate into a chromosome in the cell.

15 CSR isoforms also can be used in *ex vivo* gene expression therapy using non-viral vectors. For example, cells can be engineered to express a CSR isoform, such as by integrating a CSR isoform encoding-nucleic acid into a genomic location, either operatively linked to regulatory sequences or such that it is placed operatively linked to regulatory sequences in a genomic location. Such cells then can be administered  
20 locally or systemically to a subject, such as a patient in need of treatment.

Viral vectors, include, for example adenoviruses, herpes viruses, retroviruses and others designed for gene therapy can be employed. The vectors can remain episomal or can integrate into chromosomes of the treated subject. A CSR isoform can be expressed by a virus, which is administered to a subject in need of treatment.  
25 Virus vectors suitable for gene therapy include adenovirus, adeno-associated virus, retroviruses, lentiviruses and others noted above. For example, adenovirus expression technology is well-known in the art and adenovirus production and administration methods also are well known. Adenovirus serotypes are available, for example, from the American Type Culture Collection (ATCC, Rockville, MD). Adenovirus can be  
30 used *ex vivo*, for example, cells are isolated from a patient in need of treatment, and transduced with a CSR isoform-expressing adenovirus vector. After a suitable

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culturing period, the transduced cells are administered to a subject, locally and/or systemically. Alternatively, CSR isoform-expressing adenovirus particles are isolated and formulated in a pharmaceutically-acceptable carrier for delivery of a therapeutically effective amount to prevent, treat or ameliorate a disease or condition of a subject. Typically, adenovirus particles are delivered at a dose ranging from 1 particle to 10<sup>14</sup> particles per kilogram subject weight, generally between 10<sup>6</sup> or 10<sup>8</sup> particles to 10<sup>12</sup> particles per kilogram subject weight. In some situations it is desirable to provide a nucleic acid source with an agent that targets cells, such as an antibody specific for a cell surface membrane protein or a target cell, or a ligand for a receptor on a target cell.

A CSR isoform can be expressed by a virus and the virus administered to a subject in need of treatment. Virus vectors suitable for gene therapy include, for example, adenovirus, adeno-associated virus, retroviruses, lentiviruses. Adenovirus expression technology is well-known in the art and adenovirus production and administration methods also are well known. Adenovirus serotypes are available, for example, from the American Type Culture Collection (ATCC, Rockville, MD). Adenovirus can be used *ex vivo*, for example, cells are isolated from a patient in need of treatment, and transduced with a CSR isoform-expressing adenovirus vector. After a suitable culturing period, the transduced cells are administered to a subject, locally and/or systemically. As another example, CSR isoform-expressing adenovirus particles are isolated and formulated in a pharmaceutically-acceptable carrier for delivery of a therapeutically effective amount to prevent, treat or ameliorate a disease or condition of a subject. Typically, adenovirus particles are delivered at a dose ranging from 1 particle to 10<sup>14</sup> particles per kilogram subject weight, generally between 10<sup>6</sup> or 10<sup>8</sup> particles to 10<sup>12</sup> particles per kilogram subject weight. In some situations it is desirable to provide a nucleic acid source with an agent that targets cells, such as an antibody specific for a cell surface membrane protein or a target cell, or a ligand for a receptor on a target cell. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g. capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization

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in cycling, and proteins that target intracellular localization and enhance intracellular half-life.

**b. Artificial chromosomes and other non-viral vector delivery methods**

5 CSR isoforms also can be used in *ex vivo* gene expression therapy using non-viral vectors. For example, cells can be engineered which express a CSR isoform, such as by integrating a CSR isoform sequence into a genomic location, either operatively linked to regulatory sequences or such that it is placed operatively linked to regulatory sequences in a genomic location. Such cells then can be administered  
10 locally or systemically to a subject, such as a patient in need of treatment.

The nucleic acid molecules can be introduced into artificial chromosomes and other non-viral vectors. Artificial chromosomes (see, *e.g.*, U.S. Patent No. 6,077,697 and PCT International PCT application No. WO 02/097059) can be engineered to encode and express the isoform.

15 **c. Liposomes and other encapsulated forms and administration of cells containing the nucleic acids**

The nucleic acids can be encapsulated in a vehicle, such as a liposome, or introduced into a cells, such as a bacterial cell, particularly an attenuated bacterium or introduced into a viral vector. For example, when liposomes are employed, proteins  
20 that bind to a cell surface membrane protein associated with endocytosis can be used for targeting and/or to facilitate uptake, *e.g.* capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, and proteins that target intracellular localization and enhance intracellular half-life.

25 **2. In vitro and Ex vivo delivery**

For *ex vivo* and *in vivo* methods, nucleic acid molecules encoding the CSR isoform is introduced into cells that are from a suitable donor or the subject to be treated. *In vivo* expression of a CSR isoform can be linked to expression of additional molecules. For example, expression of a CSR isoform can be linked with  
30 expression of a cytotoxic product such as in an engineered virus or expressed in a cytotoxic virus. Such viruses can be targeted to a particular cell type that is a target

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for a therapeutic effect. The expressed a CSR isoform can be used to enhance the cytotoxicity of the virus.

*In vivo* expression of a CSR isoform can include operatively linking a CSR isoform encoding nucleic acid molecule to specific regulatory sequences such as a cell-specific or tissue-specific promoter. CSR isoforms also can be expressed from vectors that specifically infect and/or replicate in target cell types and/or tissues. Inducible promoters can be use to selectively regulate CSR isoform expression.

Cells into which a nucleic acid can be introduced for purposes of therapy encompass any desired, available cell type appropriate for the disease or condition to be treated, including but not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, *e.g.*, such as stem cells obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, and other sources thereof. Tumor cells also can be target cells for *in vivo* expression of CSR isoforms. Cells used for *in vivo* expression of an isoform also include cells autologous to the patient. Such cells can be removed from a patient, nucleic acids for expression of a CSR isoform introduced, and then administered to a patient such as by injection or engraftment.

Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes and cationic lipids (*e.g.*, DOTMA, DOPE and DC-Chol) electroporation, microinjection, cell fusion, DEAE-dextran, and calcium phosphate precipitation methods. Methods of DNA delivery can be used to express CSR isoforms *in vivo*. Such methods include liposome delivery of nucleic acids and naked DNA delivery, including local and systemic delivery such as using electroporation, ultrasound and calcium-phosphate delivery. Other techniques include microinjection, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer and spheroplast fusion.

For *ex vivo* treatment, cells from a donor compatible with the subject to be treated or the subject to be treated cells are removed, the nucleic acid is introduced into these isolated cells and the modified cells are administered to the subject.

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Treatment includes direct administration, such as, for example, encapsulated within porous membranes, which are implanted into the patient (see, *e.g.* U.S. Pat. Nos. 4,892,538 and 5,283,187). Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes and cationic lipids (*e.g.*,  
5 DOTMA, DOPE and DC-Chol) electroporation, microinjection, cell fusion, DEAE-dextran, and calcium phosphate precipitation methods. Methods of DNA delivery can be used to express CSR isoforms *in vivo*. Such methods include liposome delivery of nucleic acids and naked DNA delivery, including local and systemic delivery such as using electroporation, ultrasound and calcium-phosphate delivery.  
10 Other techniques include microinjection, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer and spheroplast fusion.

*In vivo* expression of a CSR isoform can be linked to expression of additional molecules. For example, expression of a CSR isoform can be linked with expression of a cytotoxic product such as in an engineered virus or expressed in a cytotoxic virus.  
15 Such viruses can be targeted to a particular cell type that is a target for a therapeutic effect. The expressed CSR isoform can be used to enhance the cytotoxicity of the virus.

*In vivo* expression of a CSR isoform can include operatively linking a CSR isoform encoding nucleic acid molecule to specific regulatory sequences such as a  
20 cell-specific or tissue-specific promoter. CSR isoforms also can be expressed from vectors that specifically infect and/or replicate in target cell types and/or tissues. Inducible promoters can selectively regulate CSR isoform expression.

### 3. Systemic, local and topical delivery

Nucleic acid molecules, as naked nucleic acids or in vectors, artificial  
25 chromosomes, liposomes and other vehicles can be administered to the subject by systemic administration, topical, local and other routes of administration. When systemic and *in vivo*, the nucleic acid molecule or vehicle containing the nucleic acid molecule can be targeted to a cell.

Administration also can be direct, such as by administration of a vector or cell  
30 that typically targets a cell or tissue. For example, tumor cells and proliferating cells can be targeted cells for *in vivo* expression of CSR isoforms. Cells used for *in vivo*

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expression of an isoform also include cells autologous to the patient. Such cells can be removed from a patient, nucleic acids for expression of a CSR isoform introduced, and then administered to a patient such as by injection or engraftment.

**K. CSRs and Angiogenesis**

5 CSRs participate in pathways involved in a variety of pathways, including those that participate in angiogenesis, cell proliferation, inflammatory responses, and neovascularization among others. Angiogenesis is a process by which new blood vessels are formed. It occurs in healthy individuals, such as during wound healing and in aberrant conditions, such as in tumors.. It occurs for example, in a healthy  
10 body in would healing and for restoring blood flow to tissues after injury or insult. Angiogenesis is a component of tumorigenesis, which requires the growth of blood cells to feed the growing tumorous mass. In females, angiogenesis also occurs during the monthly reproductive cycle to rebuild the uterus lining, to mature the egg during ovulation and during pregnancy to build the placenta.

15 Angiogenesis is controlled through a series of "on" and "off" switches. The primary "on" switches are angiogenesis-stimulating growth factors. The primary "off" switches" are angiogenesis inhibitors. When angiogenic growth factors are produced in excess of angiogenesis inhibitors, the balance can be in favor of blood vessel growth. When inhibitors are present in excess of stimulators, angiogenesis is stopped.  
20 A healthy body maintains a balance of angiogenesis modulators. A number of angiogenic growth factors are known. These include, for example, angiogenin, angiopoietin-1, Del-1, fibroblast growth factors: acidic (aFGF) and basic (bFGF), follistatin, granulocyte colony-stimulating factor (G-CSF), hepatocyte growth factor (HGF), scatter factor (SF), interleukin-8 (IL-8), leptin, midkine, placental growth  
25 factor, platelet-derived endothelial cell growth factor (PD-ECGF), platelet-derived growth factor-BB (PDGF-BB), pleiotrophin (PTN), progranulin, proliferin, transforming growth factor-alpha (TGF-alpha), transforming growth factor-beta (TGF-beta), tumor necrosis factor-alpha (TNF-alpha), and vascular endothelial growth factor (VEGF)/vascular permeability factor (VPF).

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### 1. Angiogenesis and disease

Cellular receptors for angiogenic factors (positive and negative) can act as points of intervention in multiple disease processes, for example, in diseases and conditions where the balance of angiogenic growth factors has been altered and/or the amount or timing of angiogenesis is altered.. For example, in some situations 'too much' angiogenesis can be detrimental, such as angiogenesis that supplies blood to tumor foci, in inflammatory responses and other aberrant angiogenic-related conditions. The growth of tumors, or sites of proliferation in chronic inflammation, generally requires the recruitment of neighboring blood vessels and vascular endothelial cells to support their metabolic requirements. This is because the diffusion is limited for oxygen in tissues. Exemplary conditions that require angiogenesis include, but are not limited to solid tumors and hematologic malignancies such as lymphomas, acute leukemia, and multiple myeloma, where increased numbers of blood vessels are observed in the pathologic bone marrow.

A critical element in the growth of primary tumors and formation of metastatic sites is the angiogenic switch: the ability of the tumor or inflammatory site to promote the formation of new capillaries from preexisting host vessels. The angiogenic switch, as used in this context, refers to disease-associated angiogenesis required for the progression of cancer and inflammatory diseases, such as rheumatoid arthritis. It is a switch that activates a cascade of physiological activities that finally result in the extension of new blood vessels to support the growth of diseased tissue. Stimuli for neo-angiogenesis include hypoxia, inflammation, and genetic lesions in oncogenes or tumor suppressors that alter disease cell gene expression.

Angiogenesis also play a role in inflammatory diseases. These diseases have a proliferative component, similar to a tumor focus. In rheumatoid arthritis, one component of this is characterized by aberrant proliferation of synovial fibroblasts, resulting in pannus formation. The pannus is composed of synovial fibroblasts which have some phenotypic characteristics with transformed cells. As a pannus grows within the joint it expresses many proangiogenic signals, and experiences many of the same neo-angiogenic requirements as a tumor. The need for additional blood supply, neoangiogenesis, is critical. Similarly, many chronic inflammatory conditions also

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have a proliferative component in which some of the cells composing it may have characteristics usually attributed to transformed cells.

Another example of a condition involving excess angiogenesis is diabetic retinopathy (Lip et al. Br J Ophthalmology 88: 1543, 2004)). Diabetic retinopathy has  
5 angiogenic, inflammatory and proliferative components; overexpression of VEGF, and angiopoietin-2 are common. This overexpression is likely required for disease-associated remodeling and branching of blood vessels, which then supports the proliferative component of the disease.

## 2. Angiogenesis

10 Angiogenesis includes several steps, including the recruitment of circulating endothelial cell precursors (CEPs), stimulation of new endothelial cell (EC) growth by growth factors, the degradation of the ECM by proteases, proliferation of ECs and migration into the target, which could be a tumor site or another proliferative site caused by inflammation. This results in the eventual formation of new capillary tubes.  
15 Such blood vessels are not necessarily normal in structure. They may have chaotic architecture and blood flow. Due to an imbalance of angiogenic regulators such as vascular endothelial growth factor, (VEGF) and angiopoietins, the new vessels supplying tumorous or inflammatory sites are tortuous and dilated with an uneven diameter, excessive branching, and shunting. Blood flow is variable, with areas of  
20 hypoxia and acidosis leading to the selection of variants that are resistant to hypoxia-induced apoptosis (often due to the loss of p53 expression); and enhanced production of proangiogenic signals. Disease-associated vessel walls have numerous openings, widened interendothelial junctions, and discontinuous or absent basement membrane; this contributes to the high vascular permeability of these vessels and, together with  
25 lack of functional lymphatics/drainage, causes interstitial hypertension. Disease-associated blood vessels may lack perivascular cells such as pericytes and smooth muscle cells that normally regulate vasoactive control in response to tissue metabolic needs. Unlike normal blood vessels, the vascular lining of tumor vessels is not a homogenous layer of ECs but often consists of a mosaic of ECs and tumor cells; the  
30 concept of cancer cell-derived vascular channels, which may be lined by ECM secreted by the tumor cells, is referred to as vascular mimicry.



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A similar situation occurs where blood vessels rapidly invade sites of acute inflammation. The ECs of angiogenic blood vessels are unlike quiescent ECs found in adult vessels, where only 0.01% of ECs are dividing. During tumor angiogenesis, ECs are highly proliferative and express a number of plasma membrane proteins that are characteristic of activated endothelium, including growth factor receptors and adhesion molecules such as integrins. Tumors utilize a number of mechanisms to promote their vascularization, and in each case they subvert normal angiogenic processes to suit this purpose. For this reason, increased production of angiogenic factors, both proliferative with respect to endothelium; and structural (allowing for increased branching of the neovasculature) are likely to occur in disease foci, as in cancer or chronic inflammatory disease.

### 3. Cell surface receptors in Angiogenesis

Cell surface receptors including RTKs, and their ligands play a role in the regulation of angiogenesis (see for example, Figure 1). Angiogenic endothelium expresses a number of receptors not found on resting endothelium. These include receptor tyrosine kinases (RTK) and integrins that bind to the extracellular matrix and mediate endothelial cells adhesion, migration, and invasion.

Endothelial cells (ECs) also express RTK (*i.e.*, the FGF and PDGF receptors) that are found on many other cell types. Functions mediated by activated RTK include proliferation, migration, and enhanced survival of endothelial cells, as well as regulation of the recruitment of perivascular cells and bloodborne circulating endothelial precursors and hematopoietic stem cells to the tumor. One example of a CSR involved in angiogenesis is VEGFR. VEGFR-1 receptors and VEGF-A ligand are involved in cell proliferation, migration and differentiation in angiogenesis. VEGF-A is a heparin-binding glycoprotein with at least four isoforms that regulate blood vessel formation by binding to RTKs, VEGFR-1 and VEGFR-2. These VEGF receptors are expressed on all ECs in addition to a subset of hematopoietic cells. VEGFR-2 regulates EC proliferation, migration, and survival, while VEGFR-1 may act as an antagonist of R1 in ECs but also can play a role in angioblast differentiation during embryogenesis.

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Additional signaling pathways also are involved in angiogenesis. The angiopoietin, Ang1, produced by stromal cells, binds to the EC RTK TEK and promotes the interaction of ECs with the ECM and perivascular cells, such as pericytes and smooth muscle cells, to form tight, non-leaky vessels. PDGF and basic  
5 fibroblast growth factor (bFGF) help to recruit these perivascular cells. Ang1 is required for maintaining the quiescence and stability of mature blood vessels and prevents the vascular permeability normally induced by VEGF and inflammatory cytokines.

Proangiogenic cytokines, chemokines, and growth factors secreted by stromal  
10 cells or inflammatory cells make important contributions to neovascularization, including bFGF, transforming growth factor- $\alpha$ , TNF- $\alpha$ , and IL-8. In contrast to normal endothelium, angiogenic endothelium overexpresses specific members of the integrin family of ECM-binding proteins that mediate EC adhesion, migration, and survival. Integrins mediate spreading and migration of ECs and are required for  
15 angiogenesis induced by VEGF and bFGF, which in turn can upregulate EC integrin expression. EC adhesion molecules can be upregulated (i.e., by VEGF, TNF- $\alpha$ ). VEGF promotes the mobilization and recruitment of circulating endothelial cell precursors (CEPs) and hematopoietic stem cells (HSCs) to tumors where they colocalize and appear to cooperate in neovessel formation. CEPs express VEGFR-2,  
20 while HSCs express VEGFR-1, a receptor, or VEGF and PlGF. Both CEPs and HSCs are derived from a common precursor, the hemangioblast. CEPs are thought to differentiate into ECs, whereas the role of HSC-derived cells (such as tumor-associated macrophages) may be to secrete angiogenic factors required for sprouting and stabilization of ECs (VEGF, bFGF, angiopoietins) and to activate MMPs,  
25 resulting in ECM remodeling and growth factor release. In mouse tumor models and in human cancers, increased numbers of CEPs and subsets of VEGFR-1 or VEGFR-expressing HSCs can be detected in the circulation, which may correlate with increased levels of serum VEGF.

#### **4. Tumor and inflammatory diseases**

30 Tumors secrete trophic angiogenic molecules, such as VEGF family of endothelial growth factors, that induce the proliferation and migration of host ECs

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into the tumor. Tumor vessels appear to be more dependent on VEGFR signaling for growth and survival than normal ECs. Sprouting in normal and pathogenic angiogenesis is regulated by three families of transmembrane RTKs expressed on ECs and their ligand: VEGFs, angiopoietins, and ephrins, which are produced by tumor cells, inflammatory cells, or stromal cells in the microenvironment of the disease site. Tumor or inflammatory disease-associated angiogenesis is a complex process involving many different cell types that proliferate, migrate, invade, and differentiate in response to signals from microenvironment. Endothelial cells (ECs) sprout from host vessels in response to VEGF, bFGF, Ang2, and other proangiogenic stimuli. Sprouting is stimulated by VEGF/VEGFR-2, Ang2/TEK, and integrin/extracellular matrix (ECM) interactions. Bone marrow-derived circulating endothelial precursors (CEPs) migrate to the tumor in response to VEGF and differentiate into ECs, while hematopoietic stem cells differentiate into leukocytes, including tumor/disease site-associated macrophages that secrete angiogenic growth factors and produce MMPs that remodel the ECM and release bound growth factors.

When tumor cells arise in or metastasize to an avascular area, they grow to a size limited by hypoxia and nutrient deprivation. This condition, also likely to occur in other localized proliferative diseases, leads to the selection of cells that produce angiogenic factors. Hypoxia, a key regulator of tumor angiogenesis, causes the transcriptional induction of the gene(s) encoding VEGF by a process that involves stabilization of the transcription factor hypoxia-inducible factor (HIF)1. Under normoxic conditions, EC HIF-1 levels are maintained at a low level by proteasome-mediated destruction regulated by a ubiquitin E3-ligase encoded by the VHL (Von Hippel-Lindau ) tumor-suppressor locus. However, under hypoxic conditions, the HIF-1 protein is not hydroxylated and association with VHL does not occur; therefore HIF-1 levels increase, and target genes including VEGF, nitric oxide synthetase (NOS), and Ang2 are induced. Loss of the VHL genes, as occurs in familial and sporadic renal cell carcinomas, also results in HIF-1 stabilization and induction of VEGF. Most tumors have hypoxic regions due to poor blood flow, and tumor cells in these areas stain positive for HIF-1 expression. These are conditions that lead to the de novo formation of blood vessels from differentiating endothelial

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cells, as occurs during embryonic development, and angiogenesis under normal (wound healing, corpus luteum formation) and pathologic processes (tumor angiogenesis, inflammatory conditions such as rheumatoid arthritis).

For diseased cell-derived VEGF, such as may be produced by a growing  
5 tumor focus or by pannus formation in rheumatoid arthritis, to initiate sprouting from host vessels, the stability conferred by the Ang1/TEK pathway must be perturbed; this occurs by the secretion of Ang2 by ECs that are undergoing active remodeling. Ang2 binds to TEK and is a competitive inhibitor of Ang1 action: under the influence of Ang2, preexisting blood vessels become more responsive to remodeling signals, with  
10 less adherence of ECs to stroma and associated perivascular cells and more responsiveness to VEGF. Therefore, Ang2 is required at early stages of neoangiogenesis for destabilizing the vasculature by making host ECs more sensitive to angiogenic signals. Since tumor ECs are blocked by Ang2, there is no stabilization by the Ang1/TEK interaction, and tumor blood vessels are leaky, hemorrhagic, and  
15 have poor association of ECs with underlying stroma. Sprouting tumor ECs express high levels of the transmembrane protein Ephrin-B2 and its receptor, the RTK EPH whose signaling appears to work with the angiopoietins during vessel remodeling. During embryogenesis, EPH receptors are expressed on the endothelium of primordial venous vessels while the transmembrane ligand ephrin-B2 is expressed by cells of  
20 primordial arteries; the reciprocal expression may regulate differentiation and patterning of the vasculature.

Development of tumor lymphatics also is associated with expression of cell surface receptors, including VEGFR-3 and its ligands VEGF-C and VEGF-D. The role of these vessels in tumor cell metastasis to regional lymph nodes remains to be  
25 determined, since, as discussed above, interstitial pressures within tumors are high and most lymphatic vessels may exist in a collapsed and nonfunctional state. However, VEGF-C levels in primary human tumors, including lung, prostate, and colorectal cancers, correlate significantly with metastasis to regional lymph nodes, and therefore it is possible that expression of VEGF-C,D/R3 may contribute to  
30 disease spreading by maintaining an exit for tumor cells from the primary site to lymph nodes and beyond.

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## **5. Cell surface receptors and treatment of angiogenic diseases and conditions**

Modulation of angiogenesis, neovascularization and/or cell proliferation can be used to treat diseases and conditions in which angiogenesis plays a role. For example, angiogenesis inhibitors can function by targeting the critical molecular pathways involved in EC proliferation, migration, and/or survival, many of which are unique to the activated endothelium in tumors. Inhibition of growth factor and adhesion-dependent signaling pathways can induce EC apoptosis with concomitant inhibition of tumor growth. ECs comprising the tumor vasculature are genetically stable and do not share genetic changes with tumor cells; the EC apoptosis pathways are therefore intact. Each EC of a tumor vessel helps provide nourishment to many tumor cells, and although tumor angiogenesis can be driven by a number of exogenous proangiogenic stimuli, experimental data indicate that blockade of a single growth factor (*e.g.*, VEGF) can inhibit tumor-induced vascular growth. Because tumor blood vessels are distinct from normal ones, they may be selectively destroyed without affecting normal vessels.

Because cell surface receptors are involved in the regulation of angiogenesis, they can be therapeutic targets for treatment of diseases and conditions involving angiogenesis. Provided herein are CSR isoforms that can modulate one or more steps in the angiogenic process. CSR isoforms can be administered singly, in parallel or in other combinations. For instance, angiogenesis induced by bFGF can be blocked by inhibitors of the bFGFR such as a CSR isoform, and this can in turn inhibit activation of the VEGF pathway. The VEGFR pathway also can be blocked by a VEGFR isoform. CSR isoforms that modulate Ang/TEK and Ephrin/EPH pathways also can be administered to modulate angiogenesis. CSR isoforms that act as antagonists of the activity of VEGFR, bFGF, Ang2, TNF-alpha, TGF-alpha, and other factors such as ephrin antagonists, can be administered. These ligands and their receptors are required for the attraction of new endothelial cells, and/or their structural transformation into blood vessels by differentiation from circulating endothelial precursors (CEPs) or by inhibiting either tube formation or the needed branching. Hence, antagonizing one or more of these factors can inhibit the development and

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progression of cancer and inflammatory disease. As described herein, CSR isoforms can be administered as therapeutics for such diseases and conditions.

**L. Exemplary Treatments and Studies with CSR isoforms**

5 Provided herein are methods of treatment with CSR isoforms for diseases and conditions. CSR isoforms such as RTK isoforms and TNFR isoforms can be used in the treatment of a variety of diseases and conditions, including those described herein. Treatment can be effected by administering by suitable route formulations of the polypeptides, which can be provided in compositions as polypeptides and can be linked to targeting agents, for targeted delivery or encapsulated in delivery vehicles, 10 such as liposomes. Alternatively, nucleic acids encoding the polypeptides can be administered as naked nucleic acids or in vectors, particularly gene therapy vectors. Gene therapy can be effected by any method known to those of skill in the art. Gene therapy can be effected *in vivo* by directly administering the nucleic acid or vector. For example, the nucleic acids can be delivered systemically, locally, topically or by 15 any suitable route. The vectors or nucleic acids can be targeted by including targeting agents in delivery vehicle, such as a virus or liposome, or they can be conjugated to a targeting agent, such as an antibody. The vectors or nucleic acids can be introduced into cells *ex vivo* by removing cells from a subject or suitable donor, introducing the vector or nucleic acid into the cells and then introducing the modified cells into the 20 subject.

The CSR isoforms provided herein can be used for treating a variety of disorders, particularly proliferative, immune and inflammatory disorders. Treatments, include, but are not limited to treatment of angiogenesis-related diseases and conditions including ocular diseases, atherosclerosis, cancer and vascular injuries, neuro- 25 degenerative diseases, including Alzheimer's disease, inflammatory diseases and conditions, including atherosclerosis, diseases and conditions associated with cell proliferation including cancers, and smooth muscle cell-associated conditions, and various autoimmune diseases. Exemplary treatments and preclinical studies are described for treatments and therapies with RTK and TNFR isoforms. Such descriptions are meant to be exemplary only and are not limited to a particular RTK or 30 TNFR isoform. The particular treatment and dosage can be determined by one of

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skill in the art. Considerations in assessing treatment include, the disease to be treated, the severity and course of the disease, whether the molecule is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to therapy, and the discretion of the attending physician.

5           **1. Angiogenesis-related conditions**

RTK isoforms including, but not limited to, VEGFR, PDGFR, TIE/TEK, EGFR, and EphA and TNFR isoforms including TNFR1 and TNFR2 can be used in treatment of angiogenesis- related diseases and conditions, such as ocular diseases and conditions, including ocular diseases involving neovascularization. Ocular  
10 neovascular disease is characterized by invasion of new blood vessels into the structures of the eye, such as the retina or cornea. It is the most common cause of blindness and is involved in approximately twenty eye diseases. In age-related macular degeneration, the associated visual problems are caused by an ingrowth of choroidal capillaries through defects in Bruch's membrane with proliferation of  
15 fibrovascular tissue beneath the retinal pigment epithelium. Angiogenic damage also is associated with diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma and retrolental fibroplasia. Other diseases associated with corneal neovascularization include, but are not limited to, epidemic keratoconjunctivitis, Vitamin A deficiency, contact lens overwear, atopic keratitis,  
20 superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phlyctenulosis, syphilis, Mycobacteria infections, lipid degeneration, chemical burns, bacterial ulcers, fungal ulcers, Herpes simplex infections, Herpes zoster infections, protozoan infections, Kaposi sarcoma, Mooren ulcer, Terrien's marginal degeneration, marginal keratolysis, rheumatoid arthritis, systemic lupus, polyarteritis,  
25 trauma, Wegeners sarcoidosis, Scleritis, Steven's Johnson disease, periphigoid radial keratotomy, and corneal graph rejection. Diseases associated with retinal/choroidal neovascularization include, but are not limited to, diabetic retinopathy, macular degeneration, sickle cell anemia, sarcoid, syphilis, pseudoxanthoma elasticum, Pagets disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic  
30 uveitis/vitritis, mycobacterial infections, Lyme's disease, systemic lupus erythematosis, retinopathy of prematurity, Eales disease, Bechets disease, infections

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causing a retinitis or choroiditis, presumed ocular histoplasmosis, Bests disease, myopia, optic pits, Stargardt's disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, trauma and post-laser complications. Other diseases include, but are not limited to, diseases associated with rubeosis

5 (neovascularization of the angle) and diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy.

RTK and TNFR isoform therapeutic effects on angiogenesis such as in treatment of ocular diseases can be assessed in animal models, for example in cornea implants, such as described herein. For example, modulation of angiogenesis such as  
10 for an RTK can be assessed in a nude mouse model such as epidermoid A431 tumors in nude mice and VEGF-or PlGF-transduced rat C6 gliomas implanted in nude mice. CSR isoforms can be injected as protein locally or systemically. Alternatively cells expressing CSR isoforms can be inoculated locally or at a site remote to the tumor. Tumors can be compared between control treated and CSR isoform treated models to  
15 observe phenotypes of tumor inhibition including poorly vascularized and pale tumors, necrosis, reduced proliferation and increased tumor-cell apoptosis. In one such treatment, Flt-1 isoforms are used to treat ocular disease and assessed in such models.

Examples of ocular disorders that can be treated with TIE/TEK isoforms are  
20 eye diseases characterized by ocular neovascularization including, but not limited to, diabetic retinopathy (a major complication of diabetes), retinopathy of prematurity (this devastating eye condition, that frequently leads to chronic vision problems and carries a high risk of blindness, is a severe complication during the care of premature infants), neovascular glaucoma, retinoblastoma, retrolental fibroplasia, rubeosis,  
25 uveitis, macular degeneration, and corneal graft neovascularization. Other eye inflammatory diseases, ocular tumors, and diseases associated with choroidal or iris neovascularization also can be treated with TIE/TEK isoforms.

PDGFR isoforms also can be used in the treatment of proliferative vitreoretinopathy. For example, an expression vector such as a retroviral vector is  
30 constructed containing a nucleic acid molecule encoding a PDGFR isoform. Rabbit conjunctival fibroblasts (RCFs) are produced which contain the expression vector by



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Additional signaling pathways also are involved in angiogenesis. The angiopoietin, Ang1, produced by stromal cells, binds to the EC RTK Tie-2 and promotes the interaction of ECs with the ECM and perivascular cells, such as pericytes and smooth muscle cells, to form tight, non-leaky vessels. PDGF and basic  
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Proangiogenic cytokines, chemokines, and growth factors secreted by stromal  
10 cells or inflammatory cells make important contributions to neovascularization, including bFGF, transforming growth factor- $\alpha$ , TNF- $\alpha$ , and IL-8. In contrast to normal endothelium, angiogenic endothelium overexpresses specific members of the integrin family of ECM-binding proteins that mediate EC adhesion, migration, and survival. Integrins mediate spreading and migration of ECs and are required for  
15 angiogenesis induced by VEGF and bFGF, which in turn can upregulate EC integrin expression. EC adhesion molecules can be upregulated (i.e., by VEGF, TNF- $\alpha$ ). VEGF promotes the mobilization and recruitment of circulating endothelial cell precursors (CEPs) and hematopoietic stem cells (HSCs) to tumors where they colocalize and appear to cooperate in neovessel formation. CEPs express VEGFR2,  
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25 resulting in ECM remodeling and growth factor release. In mouse tumor models and in human cancers, increased numbers of CEPs and subsets of VEGFR1 or VEGFR-expressing HSCs can be detected in the circulation, which may correlate with increased levels of serum VEGF.

#### 4. Tumor and inflammatory diseases

30 Tumors secrete trophic angiogenic molecules, such as VEGF family of endothelial growth factors, that induce the proliferation and migration of host ECs

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into the tumor. Tumor vessels appear to be more dependent on VEGFR signaling for growth and survival than normal ECs. Sprouting in normal and pathogenic angiogenesis is regulated by three families of transmembrane RTKs expressed on ECs and their ligand: VEGFs, angiopoietins, and ephrins, which are produced by tumor  
5 cells, inflammatory cells, or stromal cells in the microenvironment of the disease site. Tumor or inflammatory disease-associated angiogenesis is a complex process involving many different cell types that proliferate, migrate, invade, and differentiate in response to signals from microenvironment. Endothelial cells (ECs) sprout from host vessels in response to VEGF, bFGF, Ang2, and other proangiogenic stimuli.  
10 Sprouting is stimulated by VEGF/VEGFR2, Ang2/Tie-2, and integrin/extracellular matrix (ECM) interactions. Bone marrow-derived circulating endothelial precursors (CEPs) migrate to the tumor in response to VEGF and differentiate into ECs, while hematopoietic stem cells differentiate into leukocytes, including tumor/disease site-associated macrophages that secrete angiogenic growth factors and produce MMPs  
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20 transcriptional induction of the gene(s) encoding VEGF by a process that involves stabilization of the transcription factor hypoxia-inducible factor (HIF)1. Under normoxic conditions, EC HIF-1 levels are maintained at a low level by proteasome-mediated destruction regulated by a ubiquitin E3-ligase encoded by the VHL (Von Hippel-Lindau ) tumor-suppressor locus. However, under hypoxic conditions,  
25 the HIF-1 protein is not hydroxylated and association with VHL does not occur; therefore HIF-1 levels increase, and target genes including VEGF, nitric oxide synthetase (NOS), and Ang2 are induced. Loss of the VHL genes, as occurs in familial and sporadic renal cell carcinomas, also results in HIF-1 stabilization and induction of VEGF. Most tumors have hypoxic regions due to poor blood flow, and  
30 tumor cells in these areas stain positive for HIF-1 expression. These are conditions that lead to the de novo formation of blood vessels from differentiating endothelial

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cells, as occurs during embryonic development) and angiogenesis under normal (wound healing, corpus luteum formation) and pathologic processes (tumor angiogenesis, inflammatory conditions such as rheumatoid arthritis).

For diseased cell-derived VEGF, such as may be produced by a growing  
5 tumor focus or by pannus formation in rheumatoid arthritis, to initiate sprouting from host vessels, the stability conferred by the Ang1/Tie2 pathway must be perturbed; this occurs by the secretion of Ang2 by ECs that are undergoing active remodeling. Ang2 binds to Tie2 and is a competitive inhibitor of Ang1 action: under the influence of Ang2, preexisting blood vessels become more responsive to remodeling signals, with  
10 less adherence of ECs to stroma and associated perivascular cells and more responsiveness to VEGF. Therefore, Ang2 is required at early stages of neoangiogenesis for destabilizing the vasculature by making host ECs more sensitive to angiogenic signals. Since tumor ECs are blocked by Ang2, there is no stabilization by the Ang1/Tie2 interaction, and tumor blood vessels are leaky, hemorrhagic, and  
15 have poor association of ECs with underlying stroma. Sprouting tumor ECs express high levels of the transmembrane protein Ephrin-B2 and its receptor, the RTK EPH whose signaling appears to work with the angiopoietins during vessel remodeling. During embryogenesis, EPH receptors are expressed on the endothelium of primordial venous vessels while the transmembrane ligand ephrin-B2 is expressed by cells of  
20 primordial arteries; the reciprocal expression may regulate differentiation and patterning of the vasculature.

Development of tumor lymphatics also is associated with expression of cell surface receptors, including VEGFR3 and its ligands VEGF-C and VEGF-D. The role of these vessels in tumor cell metastasis to regional lymph nodes remains to be  
25 determined, since, as discussed above, interstitial pressures within tumors are high and most lymphatic vessels may exit in a collapsed and nonfunctional state. However, VEGF-C levels in primary human tumors, including lung, prostate, and colorectal cancers, correlate significantly with metastasis to regional lymph nodes, and therefore it is possible that expression of VEGF-C,D/R3 may contribute to disease spreading by  
30 maintaining an exit for tumor cells from the primary site to lymph nodes and beyond.

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### **5. Cell surface receptors and treatment of angiogenic diseases and conditions**

Modulation of angiogenesis, neovascularization and/or cell proliferation can be used to treat diseases and conditions in which angiogenesis plays a role. For example, angiogenesis inhibitors can function by targeting the critical molecular pathways involved in EC proliferation, migration, and/or survival, many of which are unique to the activated endothelium in tumors. Inhibition of growth factor and adhesion-dependent signaling pathways can induce EC apoptosis with concomitant inhibition of tumor growth. ECs comprising the tumor vasculature are genetically stable and do not share genetic changes with tumor cells; the EC apoptosis pathways are therefore intact. Each EC of a tumor vessel helps provide nourishment to many tumor cells, and although tumor angiogenesis can be driven by a number of exogenous proangiogenic stimuli, experimental data indicate that blockade of a single growth factor (e.g., VEGF) can inhibit tumor-induced vascular growth. Because tumor blood vessels are distinct from normal ones, they may be selectively destroyed without affecting normal vessels.

Because cell surface receptors are involved in the regulation of angiogenesis, they can be therapeutic targets for treatment of diseases and conditions involving angiogenesis. Provided herein are CSR isoforms that can modulate one or more steps in the angiogenic process. CSR isoforms can be administered singly, in parallel or in other combinations. For instance, angiogenesis induced by bFGF can be blocked by inhibitors of the bFGFR such as a CSR isoform, and this can in turn inhibit activation of the VEGF pathway. The VEGFR pathway also can be blocked by a VEGFR isoform. CSR isoforms that modulate Ang/Tie2 and Ephrin/EPH pathways also can be administered to modulate angiogenesis. CSR isoforms that act as antagonists of the activity of VEGFR, bFGF, Ang2, TNF-alpha, TGF-alpha, and other factors such as ephrin antagonists, can be administered. These ligands and their receptors are required for the attraction of new endothelial cells, and/or their structural transformation into blood vessels by differentiation from circulating endothelial precursors (CEPs) or by inhibiting either tube formation or the needed branching. Hence, antagonizing one or more of these factors can inhibit the development and

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progression of cancer and inflammatory disease. As described herein, CSR isoforms can be administered as therapeutics for such diseases and conditions.

**L. Exemplary Treatments and Studies with CSR isoforms**

Provided herein are methods of treatment with CSR isoforms for diseases and conditions. CSR isoforms such as RTK isoforms and TNFR isoforms can be used in the treatment of a variety of diseases and conditions, including those described herein. Treatment can be effected by administering by suitable route formulations of the polypeptides, which can be provided in compositions as polypeptides and can be linked to targeting agents, for targeted delivery or encapsulated in delivery vehicles, such as liposomes. Alternatively, nucleic acids encoding the polypeptides can be administered as naked nucleic acids or in vectors, particularly gene therapy vectors. Gene therapy can be effected by any method known to those of skill in the art. Gene therapy can be effect in vivo by directly administering the nucleic acid or vector. For example, the nucleic acids can be delivered systemically, locally, topically or by any suitable route. The vectors or nucleic acids can be targeted by including targeting agents in delivery vehicle, such as a virus or liposome, or they can be conjugated to a targeting agent, such as an antibody. The vectors or nucleic acids can be introduced into cells *ex vivo* by removing cells from a subject or suitable donor, introducing the vector or nucleic acid into the cells and then introducing the modified cells into the subject.

The CSR isoforms provided herein can be used for treating a variety of disorders, particularly proliferative, immune and inflammatory disorders. Treatments, include, but are not limited to treatment of angiogenesis-related diseases and conditions including ocular diseases, atherosclerosis, cancer and vascular injuries, neurodegenerative diseases, including Alzheimer's disease, inflammatory diseases and conditions, including atherosclerosis, diseases and conditions associated with cell proliferation including cancers, and smooth muscle cell-associated conditions, and various autoimmune diseases. Exemplary treatments and preclinical studies are described for treatments and therapies with RTK and TNFR isoforms. Such descriptions are meant to be exemplary only and are not limited to a particular RTK or TNFR isoform. The particular treatment and dosage can be determined by one of

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skill in the art. Considerations in assessing treatment include, the disease to be treated, the severity and course of the disease, whether the molecule is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to therapy, and the discretion of the attending physician.

5           1.       **Angiogenesis-related conditions**

RTK isoforms including, but not limited to, VEGFR, PDGFR, TIE/TEK, EGFR, and EphA and TNFR isoforms including TNFR1 and TNFR2 can be used in treatment of angiogenesis-related diseases and conditions, such as ocular diseases and conditions, including ocular diseases involving neovascularization. Ocular

10   neovascular disease is characterized by invasion of new blood vessels into the structures of the eye, such as the retina or cornea. It is the most common cause of blindness and is involved in approximately twenty eye diseases. In age-related macular degeneration, the associated visual problems are caused by an ingrowth of choroidal capillaries through defects in Bruch's membrane with proliferation of

15   fibrovascular tissue beneath the retinal pigment epithelium. Angiogenic damage also is associated with diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma and retrolental fibroplasia. Other diseases associated with corneal neovascularization include, but are not limited to, epidemic keratoconjunctivitis, Vitamin A deficiency, contact lens overwear, atopic keratitis,

20   superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phlyctenulosis, syphilis, Mycobacteria infections, lipid degeneration, chemical burns, bacterial ulcers, fungal ulcers, Herpes simplex infections, Herpes zoster infections, protozoan infections, Karposi sarcoma, Mooren ulcer, Terrien's marginal degeneration, marginal keratolysis, rheumatoid arthritis, systemic lupus, polyarteritis,

25   trauma, Wegeners sarcoidosis, Scleritis, Steven's Johnson disease, periphigoid radial keratotomy, and corneal graph rejection. Diseases associated with retinal/choroidal neovascularization include, but are not limited to, diabetic retinopathy, macular degeneration, sickle cell anemia, sarcoid, syphilis, pseudoxanthoma elasticum, Pagets disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic

30   uveitis/vitritis, mycobacterial infections, Lyme's disease, systemic lupus erythematosus, retinopathy of prematurity, Eales disease, Bechets disease, infections

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causing a retinitis or choroiditis, presumed ocular histoplasmosis, Bests disease, myopia, optic pits, Stargardt's disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, trauma and post-laser complications. Other diseases include, but are not limited to, diseases associated with rubeosis

5 (neovascularization of the angle) and diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy.

RTK and TNFR isoform therapeutic effects on angiogenesis such as in treatment of ocular diseases can be assessed in animal models, for example in cornea implants, such as described herein. For example, modulation of angiogenesis such as  
10 for an RTK can be assessed in a nude mouse model such as epidermoid A431 tumors in nude mice and VEGF-or PIGF-transduced rat C6 gliomas implanted in nude mice. CSR isoforms can be injected as protein locally or systemically, Alternatively cells expressing CSR isoforms can be inoculated locally or at a site remote to the tumor. Tumors can be compared between control treated and CSR isoform treated models to  
15 observe phenotypes of tumor inhibition including poorly vascularized and pale tumors, necrosis, reduced proliferation and increased tumor-cell apoptosis. In one such treatment, Flt-1 isoforms are used to treat ocular disease and assessed in such models.

Examples of ocular disorders that can be treated with TIE/TEK isoforms are  
20 eye diseases characterized by ocular neovascularization including, but not limited to, diabetic retinopathy (a major complication of diabetes), retinopathy of prematurity (this devastating eye condition, that frequently leads to chronic vision problems and carries a high risk of blindness, is a severe complication during the care of premature infants), neovascular glaucoma, retinoblastoma, retrolental fibroplasia, rubeosis,  
25 uveitis, macular degeneration, and corneal graft neovascularization. Other eye inflammatory diseases, ocular tumors, and diseases associated with choroidal or iris neovascularization also can be treated with TIE/TEK isoforms.

PDGFR isoforms also can be used in the treatment of proliferative vitreoretinopathy. For example, an expression vector such as a retroviral vector is  
30 constructed containing a nucleic acid molecule encoding a PDGFR isoform. Rabbit conjunctival fibroblasts (RCFs) are produced which contain the expression vector by

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transfection, such for a retrovirus vector, or by transformation, such as for a plasmid or chromosomal based vector. Expression of PDGFR isoform can be monitored in cells by means known in the art including use of an antibody which recognizes PDGFR isoform and by use of a peptide tag (*e.g.* a myc tag) and corresponding  
5 antibody. RCFs are injected into the vitreous part of an eye. For example, in a rabbit animal model, approximately  $1 \times 10^5$  RCFs are injected by gas vitreomy. Retrovirus expressing PDGFR isoform,  $\sim 2 \times 10^7$  CFU is injected on the same day. Effects on proliferative vitreoretinopathy can be observed, for example, 2-4 weeks following surgery, such as attenuation of the disease symptoms.

10 EphA isoforms can be used to treat diseases or conditions with misregulated and/or inappropriate angiogenesis, such as in eye diseases. For example, an EphA isoform can be assessed in an animal model such as a mouse corneal model for effects on ephrinA-1 induced angiogenesis. Hydron pellets containing ephrinA-1 alone or with EphA isoform protein are implanted in mouse cornea. Visual observations are  
15 taken on days following implantation to observe EphA isoform inhibition or reduction of angiogenesis. Anti-angiogenic treatments and methods such as described for VEGFR isoforms are applicable to EphA isoforms.

## 2. Angiogenesis related atherosclerosis

RTK isoforms, for example VEGFR Flt-1 and TIE/TEK isoforms, can be  
20 used to treat angiogenesis conditions related to atherosclerosis such as neovascularization of atherosclerosis plaques. Plaques formed within the lumen of blood vessels have been shown to have angiogenic stimulatory activity. VEGF expression in human coronary atherosclerotic lesions is associated with the progression of human coronary atherosclerosis.

25 Animal models can be used to assess RTK isoforms in treatment of atherosclerosis. Apolipoprotein-E deficient mice ( $\text{ApoE}^{-/-}$ ) are prone to atherosclerosis. Such mice are treated by injecting an RTK isoform, for example a VEGFR isoform, such as a Flt-1 intron fusion protein over a time course such as for 5 weeks starting at 5, 10 and 20 weeks of age. Lesions at the aortic root are assessed  
30 between control  $\text{ApoE}^{-/-}$  mice and isoform-treated  $\text{ApoE}^{-/-}$  mice to observe reduction of atherosclerotic lesions in isoform-treated mice.



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### 3. Additional Angiogenesis-related treatments

RTK isoforms such as VEGFR isoforms, for example, Flt1 isoforms, and EphA isoforms also can be used to treat angiogenic and inflammatory-related conditions such as proliferation of synoviocytes, infiltration of inflammatory cells, cartilage destruction and pannus formation, such as are present in rheumatoid arthritis (RA). An autoimmune model of collagen type- II induced arthritis, such as polyarticular arthritis induced in mice, can be used as a model for human RA. Mice treated with a VEGFR isoform, such as by local injection of protein, can be observed for reduction of arthritic symptoms including paw swelling, erythema and ankylosis. Reduction in synovial angiogenesis and synovial inflammation also can be observed.

Other angiogenesis-related conditions amenable to treatment with VEGFR isoforms include hemangioma. One of the most frequent angiogenic diseases of childhood is the hemangioma. In most cases, the tumors are benign and regress without intervention. In more severe cases, the tumors progress to large cavernous and infiltrative forms and create clinical complications. Systemic forms of hemangiomas, the hemangiomatoses, have a high mortality rate. Many cases of hemangiomas exist that cannot be treated or are difficult to treat with therapeutics currently in use.

VEGFR isoforms can be employed in the treatment of such diseases and conditions where angiogenesis is responsible for damage such as in Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia. This is an inherited disease characterized by multiple small angiomas, tumors of blood or lymph vessels. The angiomas are found in the skin and mucous membranes, often accompanied by epistaxis (nosebleeds) or gastrointestinal bleeding and sometimes with pulmonary or hepatic arteriovenous fistula. Diseases and disorders characterized by undesirable vascular permeability also can be treated by VEGFR isoforms. These include edema associated with brain tumors, ascites associated with malignancies, Meigs' syndrome, lung inflammation, nephrotic syndrome, pericardial effusion and pleural effusion.

Angiogenesis also is involved in normal physiological processes such as reproduction and wound healing. Angiogenesis is an important step in ovulation and also in implantation of the blastula after fertilization. Modulation of angiogenesis by VEGFR isoforms can be used to induce amenorrhea, to block ovulation or to prevent

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implantation by the blastula. VEGFR isoforms also can be used in surgical procedures. For example, in wound healing, excessive repair or fibroplasia can be a detrimental side effect of surgical procedures and may be caused or exacerbated by angiogenesis. Adhesions are a frequent complication of surgery and lead to problems  
5 such as small bowel obstruction.

PDGFR isoforms can be used in the regulation of neointima formation after arterial injury such as in arterial surgery. For example PDGFR-B isoforms can be used to regulate PDGF-BB induced cell proliferation such as involved in neointima formation. PDGFR isoforms can be assessed for example, in a balloon-injured rooster  
10 femoral artery model. An adenovirus vector expressing a PDGFR isoform is constructed and transduced *in vivo* in the arterial model. Neointima-associated thrombosis is assessed in the transduced arteries to observe reduction compared with controls.

RTK isoforms useful in treatment of angiogenesis-related diseases and  
15 conditions also can be used in combination therapies such as with anti-angiogenesis drugs, molecules which interact with other signaling molecules in RTK-related pathways, including modulation of VEGFR ligands. For example, the known anti-rheumatic drug, bucillamine (BUC), was shown to include within its mechanism of action the inhibition of VEGF production by synovial cells. Anti-rheumatic effects of  
20 BUC are mediated by suppression of angiogenesis and synovial proliferation in the arthritic synovium through the inhibition of VEGF production by synovial cells. Combination therapy of such drugs with VEGFR isoforms can allow multiple mechanisms and sites of action for treatment.

#### 4. Cancers

25 RTK isoforms such as isoforms of EGFR, TIE/TEK, VEGFR and FGFR can be used in treatment of cancers. RTK isoforms including, but not limited to, EGFR RTK isoforms, such as ErbB2 and ErbB3 isoforms, VEGFR isoforms such as Flt1 isoforms, FGFR isoforms such as FGFR-4 isoforms, and EphA1 isoforms can be used to treat cancer. Examples of cancer to be treated herein include, but are not limited to,  
30 carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. Additional examples of such cancers include squamous cell cancer (e.g. epithelial

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squamous cell cancer), lung cancer including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, as well as head and neck cancer. Combination therapies can be used with EGFR isoforms including anti-hormonal compounds, cardioprotectants, and anti-cancer agents such as chemotherapeutics and growth inhibitory agents.

Cancers treatable with EGFR isoforms generally are those that expressing an EGFR receptor or a receptor with which an EGF ligand interacts. Such cancers are known to those of skill in the art and/or can be identified by any means known in the art for detecting EGFR expression. An example of an ErbB2 expression diagnostic/prognostic assay available includes HERCEPTEST.RTM. (Dako). Paraffin embedded tissue sections from a tumor biopsy are subjected to the IHC assay and accorded a ErbB2 protein staining intensity criteria. Tumors accorded with less than a threshold score can be characterized as not overexpressing ErbB2, whereas those tumors with greater than or equal to a threshold score can be characterized as overexpressing ErbB2. In one example of treatment, ErbB2-overexpressing tumors are assessed as candidates for treatment with an EGFR isoform such as an ErbB2 isoform.

Isoforms provided herein can be used for treatment of cancers. For example, TIE/TEK isoforms can be used in the treatment of cancers such as by modulating tumor-related angiogenesis. Vascularization is involved in regulating cancer growth and spread. For example, inhibition of angiogenesis and neovascularization inhibits solid tumor growth and expansion. Tie/Tek receptors such as TEK have been shown to influence vascular development in normal and cancerous tissues. TIE/TEK isoforms can be used as an inhibitor of tumor angiogenesis. A TIE/TEK isoform is produced such as by expression of the protein in cells. For example, secreted forms

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of TIE/TEK isoform can be expressed in cells and harvested from the media. Protein can be purified or partially-purified by biochemical means known in the art and by uses of antibody purification, such as antibodies raised against TIE/TEK isoform or a portion thereof or by use of a tagged TIE/TEK isoform and a corresponding antibody.

5 Effects on angiogenesis can be monitored in an animal model such as by treating rat cornea with TIE/TEK isoform formulated as conditioned media in hydron pellets surgically implanted into a micropocket of a rat cornea or as purified protein (*e.g.* 100 µg/dose) administered to the window chamber. For example, rat models such as F344 rats with avascular corneas can be used in combination with tumor-cell conditioned  
10 media or by implanting a fragment of a tumor into the window chamber of an eye to induce angiogenesis. Corneas can be examined histologically to detect inhibition of angiogenesis induced by tumor-cell conditioned media. TIE/TEK isoforms also can be used to treat malignant and metastatic conditions such as solid tumors, including primary and metastatic sarcomas and carcinomas.

15 FGFR-4 isoforms can be used to treat cancers, for example pituitary tumors. Animal models can be used to mimic progression of human pituitary tumor progress. For example, an N-terminally shortened form of FGFR, ptd-FGFR-4, expressed in transgenic mice recapitulates pituitary tumorigenesis (Ezzat *et al.* (2002) *J. Clin. Invest.* 109:69-78), including pituitary adenoma formation in the absence of prolonged  
20 and massive hyperplasia. FGFR-4 isoforms can be administered to ptd-FGFR-4 mice and the pituitary architecture and course of tumor progression compared with control mice.

#### 5. Alzheimer's disease

Receptor isoforms, such as EGFR isoforms, also can be used to treat  
25 inflammatory conditions and other conditions involving such responses, such as Alzheimer's disease and related conditions. A variety of mouse models are available for human Alzheimer's disease including transgenic mice overexpressing mutant amyloid precursor protein and mice expressing familial autosomal dominant-linked PS1 and mice expressing both proteins (PS1 M146L/APPK670N:M671L).  
30 Alzheimer's models are treated such as by injection of ErbB isoforms. Plaque development can be assessed such as by observation of neuritic plaques in the

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hippocampus, entorhinal cortex, and cerebral cortex, using staining and antibody immunoreactivity assays.

**6. Smooth Muscle Proliferative-related diseases and conditions**

CSR isoforms, including EGFR isoforms, such as ErbB isoforms, can be  
5 employed for the treatment of a variety of diseases and conditions involving smooth muscle cell proliferation in a mammal, such as a human. An example is treatment of cardiac diseases involving proliferation of vascular smooth muscle cells (VSMC) and leading to intimal hyperplasia such as vascular stenosis, restenosis resulting from angioplasty or surgery or stent implants, atherosclerosis and hypertension. In such  
10 conditions, an interplay of various cells and cytokines released act in autocrine, paracrine or juxtacrine manner, which result in migration of VSMCs from their normal location in media to the damaged intima. The migrated VSMCs proliferate excessively and lead to thickening of intima, which results in stenosis or occlusion of blood vessels. The problem is compounded by platelet aggregation and deposition at  
15 the site of lesion. Alpha-thrombin, a multifunctional serine protease, is concentrated at sites of vascular injury and stimulates VSMC proliferation. Following activation of this receptor, VSMCs produce and secrete various autocrine growth factors, including PDGF-AA, HB-EGF and TGF. EGFRs are involved in signal transduction cascades that ultimately result in migration and proliferation of fibroblasts and VSMCs, as  
20 well as stimulation of VSMCs to secrete various factors that are mitogenic for endothelial cells and induction of chemotactic responses in endothelial cells. Treatment with EGFR isoforms can be used to modulate such signaling and responses.

EGFR isoforms such as ErbB2 and ErbB3 isoforms can be used to treat  
25 conditions where EGFRs such as ErbB2 and ErbB3 modulate bladder SMCs, such as bladder wall thickening that occurs in response to obstructive syndromes affecting the lower urinary tract. EGFR isoforms can be used in controlling proliferation of bladder smooth muscle cells, and consequently in the prevention or treatment of urinary obstructive syndromes.

30 EGFR isoforms can be used to treat obstructive airway diseases with underlying pathology involving smooth muscle cell proliferation. One example is

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asthma which manifests in airway inflammation and bronchoconstriction. EGF has been shown to stimulate proliferation of human airway SMCs and is likely to be one of the factors involved in the pathological proliferation of airway SMCs in obstructive airway diseases. EGFR isoforms can be used to modulate effects and responses to  
5 EGF by EGFRs.

#### 7. Inflammatory diseases

CSR isoforms such as TNFR isoforms can be used in the treatment of inflammatory diseases including central nervous system diseases (CNS), autoimmune diseases, airway hyper-responsiveness conditions such as in asthma, rheumatoid  
10 arthritis and inflammatory bowel disease.

TNF  $\alpha$  and LT are proinflammatory cytokines and critical mediators in inflammatory responses in diseases and conditions such as multiple sclerosis. TNF  $\alpha$  and LT- $\alpha$  are produced by infiltrating lymphocytes and macrophages and additionally by activated CNS parenchymal cells, microglial cells and astrocytes. In MS patients,  
15 TNF- $\alpha$  is overproduced in serum and cerebrospinal fluid. In lesions, TNF- $\alpha$  and TNFR are extensively expressed. TNF  $\alpha$  and LT- $\alpha$  can induce selective toxicity of primary oligodendrocytes and induce myelin damage in CNS tissues. Thus, these two cytokines have been implicated in demyelination.

Experimental autoimmune encephalomyelitis (EAE) can serve as a model  
20 for multiple sclerosis (MS) ( see for example, Probert *et al.* (2000) *Brain* 123: 2005-2019). EAE can be induced in a number of genetically susceptible species by immunization with myelin and myelin components such as myelin basic protein, proteolipid protein and myelin oligodendrocyte glycoprotein (MOG). For example, MOG-induced EAE recapitulates essential features of human MS including the  
25 chronic, relapsing clinical disease course of the pathohistological triad of inflammation, reactive gliosis, and the formation of large confluent demyelinated plaques. Additional MS models include transgenic mice overexpressing TNF  $\alpha$ , which model non-autoimmune mediated MS. Transgenic mice are engineered to express TNF  $\alpha$  locally in glial cells; human and murine TNF  $\alpha$  trigger MS-like  
30 symptoms. TNFR isoforms can be assessed in EAE animal models. Isoforms are administered, such as

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by injection, and the course and progression of symptoms is monitored compared to control animals.

Cytokines such as TNF  $\alpha$  also are involved in airway smooth muscle contractile properties. TNFR1 and TNFR2 play a role in modulating biological  
5 affects in airway smooth muscle. TNFR2 modulates calcium homeostasis and thereby modulates airway smooth muscle hyper-responsiveness. TNFR1 modulates effects of TNF  $\alpha$  in airway smooth muscle. Airway smooth muscle responses can be assessed in murine tracheal rings induced with carbachol. Effects, such as carbachol-induced contraction, in the presence and absence of TNF  $\alpha$  can be monitored. TNFR isoforms  
10 can be added to tracheal rings to assess the effects of isoforms on airway smooth muscle.

TNF  $\alpha$ /TNFRs modulate inflammation in diseases such as rheumatoid arthritis (RA) (Edwards *et al.* (2003) *Adv Drug Deliv. Rev.* 55(10):1315-36). TNFR isoforms, including TNFR1 isoforms, can be used to treat RA. For example, TNFR isoforms  
15 can be injected locally or systemically. Isoforms can be dosed daily or weekly. PEGylated TNFR isoforms can be used to reduce immunogenicity. Primate models are available for RA treatments. Response of tender and swollen joints can be monitored in subjects treated with TNFR isoforms and controls to assess TNFR isoform treatment.

## 20 8. Combination Therapies

CSR isoforms such as RTK isoforms can be used in combination with each other and with other existing drugs and therapeutics to treat diseases and conditions. For example, as described herein a number of RTK-isoforms can be used to treat angiogenesis-related conditions and diseases and/or control tumor proliferation. Such  
25 treatments can be performed in conjunction with anti-angiogenic and/or anti-tumorigenic drugs and/or therapeutics. Examples of anti-angiogenic and anti-tumorigenic drugs and therapies useful for combination therapies include tyrosine kinase inhibitors and molecules capable of modulating tyrosine kinase signal transduction including, but not limited to, 4-aminopyrrolo[2,3-d]pyrimidines (see for  
30 example, U.S. Pat. No. 5,639,757), and quinazoline compounds and compositions (e.g., U.S. Pat. No. 5,792,771). Other

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compounds useful in combination therapies include steroids such as the angiostatic 4,9(11)-steroids and C21-oxygenated steroids, angiostatin, endostatin, vasculostatin, canstatin and maspin, angiopoietins, bacterial polysaccharide CM101 and the antibody LM609 (U.S. Pat. No. 5,753,230), thrombospondin (TSP-1), platelet factor 4  
5 (PF4), interferons, metalloproteinase inhibitors, pharmacological agents including AGM-1470/TNP-470, thalidomide, and carboxyamidotriazole (CAI), cortisone such as in the presence of heparin or heparin fragments, anti-Invasive Factor, retinoic acids and paclitaxel (U.S. Pat. No. 5,716,981; incorporated herein by reference), shark cartilage extract, anionic polyamide or polyurea oligomers, oxindole derivatives,  
10 estradiol derivatives and thiazolopyrimidine derivatives.

Treatment of cancers including treatment of cancers overexpressing an EGFR can include combination therapy with an anticancer agent, a chemotherapeutic agent and growth inhibitory agent, including coadministration of cocktails of different chemotherapeutic agents. Examples of chemotherapeutic agents include taxanes  
15 (such as paclitaxel and doxorubicin) and anthracycline antibiotics. Preparation and dosing schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy also are described in Chemotherapy Service Ed., M. C. Perry, Williams & Wilkins, Baltimore, Md. (1992).

20 Additional compounds can be used in combination therapy with RTK isoforms. Anti-hormonal compounds can be used in combination therapies, such as with EGFR isoforms. Examples of such compounds include an anti-estrogen compound such as tamoxifen; an anti-progesterone such as onapristone and an anti-androgen such as flutamide, in dosages known for such molecules. It also can be  
25 beneficial to also coadminister a cardioprotectant (to prevent or reduce myocardial dysfunction that can be associated with therapy) or one or more cytokines. In addition to the above therapeutic regimes, the patient may be subjected to surgical removal of cancer cells and/or radiation therapy.

Adjuvants and other immune modulators can be used in combination with  
30 CSR isoforms in treating cancers, for example to increase immune response to tumor cells. Combination therapy can increase the effectiveness of treatments and in some



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cases, create synergistic effects such the combination is more effective than the additive effect of the treatments separately. Examples of adjuvants include, but are not limited to, bacterial DNA, nucleic acid fraction of attenuated mycobacterial cells (BCG; *Bacillus-Calmette-Guerin*), synthetic oligonucleotides from the BCG genome, and synthetic oligonucleotides containing CpG motifs (CpG ODN; Wooldridge *et al.* (1997) *Blood* 89:2994-2998), levamisole, aluminum hydroxide (alum), BCG, Incomplete Freud's Adjuvant (IFA), QS-21 (a plant derived immunostimulant), keyhole limpet hemocyanin (KLH), and dinitrophenyl (DNP). Examples of immune modulators include but are not limited to, cytokines such as interleukins (*e.g.*, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-16, IL-17, IL-18, IL-1 $\alpha$ , IL-1 $\beta$ , and IL-1 RA), granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), oncostatin M, erythropoietin, leukemia inhibitory factor (LIF), interferons, B7.1 (also known as CD80), B7.2 (also known as B70, CD86), TNF family members (TNF- $\alpha$ , TNF- $\beta$ , LT- $\beta$ , CD40 ligand, Fas ligand, CD27 ligand, CD30 ligand, 4-1BBL, Trail), and MIF, interferon, cytokines such as IL-2 and IL-12; and chemotherapy agents such as methotrexate and chlorambucil.

#### 9. Preclinical studies

Model animal studies can be used in preclinical evaluation of RTK isoforms that are candidate therapeutics. Parameters that can be assessed include, but are not limited to efficacy and concentration-response, safety, pharmacokinetics, interspecies scaling and tissue distribution. Model animal studies include assays such as described herein as well as those known to one of skill in the art. Animal models can be used to obtain data that then can be extrapolated to human dosages for design of clinical trials and treatments with RTK isoforms. For example, efficacy and concentration-response VEGFR inhibitors in tumor-bearing mice can be extrapolated to human treatment (Mordenti *et al.*, (1999) *Toxicol Pathol. Jan-Feb;27(1):14-21*) in order to define clinical dosing regimens effective to maintain a therapeutic inhibitor, such as an antibody against VEGFR for human use in the required efficacious range. Similar models and dose studies can be applied to VEGFR isoform dosage determination and translation into appropriate human doses, as well as other techniques known to the

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skilled artisan. Preclinical safety studies and preclinical pharmacokinetics can be performed, for example in monkeys, mice, rats and rabbits. Pharmacokinetic data from mice, rats and monkeys has been used to predict the pharmacokinetics of the counterpart therapeutic in human using allometric scaling. Accordingly, appropriate dosage information can be determined for the treatment of human pathological conditions, including rheumatoid arthritis, ocular neovascularization and cancer. A humanized version of the anti-VEGF antibody has been employed in clinical trials as an anti-cancer agent (Brem, (1998) *Cancer Res.* 58(13):2784-92; Presta *et al.*, (1997) *Cancer Res.* 57(20):4593-9) and such clinical data also can be considered as a reference source when designing therapeutic doses for VEGFR isoforms.

**M. Combination Therapies**

CSR isoforms, including those provided herein, can be used in combination with each other, with other cell surface receptor isoforms, such as a herstatin or any described, for example, in U.S. Application Serial Nos. 09/942,959, 09/234,208, 09/506,079; U.S. Provisional Application Serial Nos. 60/571,289, 60/580,990 and 60/666,825; and U.S. Patent No. 6,414,130, published International PCT application No. WO 00/44403, WO 01/61356, WO 2005/016966, including but not limited to, those set forth in SEQ ID Nos. 320-359; and/or with other existing drugs and therapeutics to treat diseases and conditions, particularly those involving aberrant angiogenesis and/or neovascularization, including, but not limited to, cancers and other proliferative disorders, inflammatory diseases, autoimmune disorders, as set forth herein and known to those of skill in the art.

For example, a CSR isoform, such as a VEGF isoform, can be administered with an agent for treatment of diabetes. Such agents include agents for the treatment of any or all conditions such as diabetic periodontal disease, diabetic vascular disease, tubulointerstitial disease and diabetic neuropathy. In another example, a CSR isoform is administered with an agent that treats cancers including squamous cell cancer (*e.g.* epithelial squamous cell cancer), lung cancer including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer,

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ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, as well as head and neck  
5 cancer. Any of the CSR isoforms can be administered in combination with two or more agents for treatment of a disease or a condition.

Adjuvants and other immune modulators can be used in combination with isoforms in treating cancers, for example to increase immune response to tumor cells. Combination therapy can increase the effectiveness of treatments and in some cases,  
10 create synergistic effects such the combination is more effective than the additive effect of the treatments separately. Examples of adjuvants include, but are not limited to, bacterial DNA, nucleic acid fraction of attenuated mycobacterial cells (BCG; Bacillus-Calmette-Guerin), synthetic oligonucleotides from the BCG genome, and synthetic oligonucleotides containing CpG motifs (CpG ODN; Wooldridge et al.  
15 (1997) Blood 89:2994-2998), levamisole, aluminum hydroxide (alum), BCG, Incomplete Freud's Adjuvant (IFA), QS-21 (a plant derived immunostimulant), keyhole limpet hemocyanin (KLH), and dinitrophenyl (DNP). Examples of immune modulators include but are not limited to, cytokines such as interleukins (*e.g.*, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-16, IL-17, IL-  
20 18, IL-1 $\alpha$ , IL-1 $\beta$ , and IL-1 RA), granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), oncostatin M, erythropoietin, leukemia inhibitory factor (LIF), interferons, B7.1 (also known as CD80), B7.2 (also known as B70, CD86), TNF family members (TNF- $\alpha$ , TNF- $\beta$ , LT- $\beta$ , CD40 ligand, Fas ligand, CD27 ligand, CD30 ligand, 4-1BBL, Trail), and MIF,  
25 interferon, cytokines such as IL-2 and IL-12; and chemotherapy agents such as methotrexate and chlorambucil.

Combinations of different CSR isoforms including with herstatins and other agents, can be used for treating cancers and other disorders involving aberrant angiogenesis (see, *e.g.* Fig.1 outlining targets in the angiogenesis and neovascu-  
30 larization pathway for such polypeptides and those described herein and in the above-noted copending and published applications U.S. Application Serial Nos. 09/942,959,

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09/234,208, 09/506,079; U.S. Provisional Application Serial Nos. 60/571,289, 60/580,990 and 60/666,825; and U.S. Patent No. 6,414,130, published International PCT application No. WO 00/44403, WO 01/61356, WO 2005/016966 are provided. The cell surface receptors include receptor tyrosine kinases, such as members of the VEGFR, FGFR, PDGFR (including  $R\alpha$ ,  $R\beta$ , CSF1R, Kit), Met (including c-Met, c-  
5 RON), TEK and EphA2 families. These also include ErbB2, ErbB3, ErbB4, DDR1, DDR2, EphA, EphB, FGFR-2, FGFR-3, FGFR-4, MET, PDGFR, TEK, Tie-1, KIT, ErbB2, VEGFR-1, VEGFR-2, VEGFR-3, Flt1, Flt3, TNFR1, TNFR2, RON, CSFR. Exemplary of such isoforms are the herstatins (see, SEQ ID Nos. 320-345),  
10 polypeptides that include the intron portion of a herstatin as well as any isoforms provided herein. The combinations of isoforms and/or drug agent selected is a function of the disease to be treated and is based upon consideration of the target tissues and cells and receptors expressed thereon.

The combinations, for example, can target two or more cell surface receptors  
15 or steps in the angiogenic and/or endothelial cell maintenance pathways or can target two or more cell surface receptors or steps in a disease process, such as any which one or both of these pathways are implicated, such as inflammatory diseases, tumors and all other noted herein and known to those of skill in the art. The two or more agents can be administered as a single composition or can be administered as two or more  
20 compositions (where there are more than two agents) simultaneously, intermittently or sequentially. They can be packaged as a kit that contains two or more compositions separately or as a combined composition and optionally with instructions for administration and/or devices for administration, such as syringes

The following examples are included for illustrative purposes only and are not  
25 intended to limit the scope of the invention.

## **N. EXAMPLES**

### **Example 1**

#### **Method for cloning CSR isoforms**

##### **A. Preparation of messenger RNA**

30 mRNA isolated from major human tissue types from healthy or diseased tissues or cell lines were purchased from Clontech (BD Biosciences, Clontech, Palo

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Alto, CA) and Stratagene (La Jolla, CA). Equal amounts of mRNA were pooled and used as templates for reverse transcription-based PCR amplification (RT-PCR).

#### B. cDNA synthesis

mRNA was denatured at 70°C in the presence of 40% DMSO for 10 min and quenched on ice. First-strand cDNA was synthesized with either 200 ng oligo(dT) or 20 ng random hexamers in a 20-μl reaction containing 10% DMSO, 50 mM Tris-HCl (pH 8.3), 75 mM KCl, 3 mM MgCl<sub>2</sub>, 10 mM DTT, 2mM each dNTP, 5 μg mRNA, and 200 units of Stratascript reverse transcriptase (Stratagene, La Jolla, CA). After incubation at 37°C for 1 h, the cDNA from both reactions were pooled and treated with 10 units of RNase H (Promega, Madison, WI).

#### C. PCR amplification

Gene-specific PCR primers were selected using the Oligo 6.6 software (Molecular Biology Insights, Inc., Cascade, CO) and synthesized by Qiagen-Operon (Richmond, CA). The forward primers flank the start codon. The reverse primers flank the stop codon or were chosen from regions at least 1.5 kb downstream from the start codon (see Table 4). Each PCR reaction contained 10 ng of reverse-transcribed cDNA, 0.025 U/μl TaqPlus (Stratagene), 0.0035 U/μl PfuTurbo (Stratagene), 0.2 mM dNTP (Amersham, Piscataway, NJ), and 0.2 μM forward and reverse primers in a total volume of 50 μl. PCR conditions were 35 cycles and 94.5°C for 45 s, 58°C for 50 s, and 72°C for 5 min. The reaction was terminated with an elongation step of 72°C for 10 min.

**TABLE 3B: LIST OF GENES FOR CLONING CSR Isoforms**

Family	Member	nt ACC. #	Catalytic Domain	SEQ ID NO:	ORF	ppt ACC.#	SEQ ID NO:
PDGFR	CSF1R	NM_005211	2012-3208	162	293-3211	NP_005202	249
	FIt3	NM_004119	1861-2886	244	58-3039	NP_004110	272
	KIT	NM_000222	1762-2799	1	22-2952	NP_000213	273
	PDGFR-A	NM_006206	2147-3253	246	395-3664	NP_006197	275
	PDGFR-B	NM_002609	2133-3215	163	357-3677	NP_002600	276
DDR	DDR1	NM_013993	2149-	156	337-	NP_054699	250

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Family	Member	nt ACC. #	Catalytic Domain	SEQ ID NO:	ORF	pnt ACC.#	SEQ ID NO:
	DDR2	NM_006182	3057 2022-2900	227	3078 354-2921	NP_006173	251
EPH	EphA1	NM-005232	1939-2736	165	88-3018	NP_005223	253
	EphA2	NM-004431	1956-2759	229	138-3068	NP_004422	254
	EphA3	NM-005233	2086-2859	230	226-3177	NP_005224	255
	EphA4	NM_004438	1885-2685	231	43-3003	NP_004429	256
	EphA5	L36644	1259-1460	232	1-2976	AAA74245	257
	EphA6	AL133666	691-1332	233	343-1347	CAB63775	258
	EphA7	NM_004440	2092-2892	234	214-3210	NP_004431	259
	EphA8	NM_020526	2028-2801	235	126-3143	NP_065387	260
	EphB1	NM_004441	2051-2857	166	215-3169	NP_004432	261
	EphB2	AF025304	1886-2681	236	26-3193	AAB94602	262
	EphB3	NM_004443	2316-3122	237	438-3434	NP_004434	263
	EphB4	NM_004444	2200-3006	238	376-3339	NP_004435	264
	EphB6	NM_004445	2761-3498	239	799-3819	NP_004436	265
ERB	ErbB2	NM_004448	2396-3164	240	239-4006	NP_004439	266
	ErbB3	NM_001982	2318-3086	241	194-4222	NP_001973	267
	EGFR	NM_005228	2380-3148	228	247-3879	NP_005219	252
FGFR	FGFR-1	M34641	1435-2263	164	10-2472	AAA35835	268
	FGFR-2	NM_000141	2009-2872	242	593-3058	NP_000132	269
	FGFR-3	NM_000142	1429-2292	243	40-2460	NP_000133	270
	FGFR-4	NM_002011	1534-2394	2	157-2565	NP_002002	271
MET	MET	NM_000245	3419-4198	245	188-4360	NP_000236	274
	RON	NM_002447	3242-4260	159	29-4231	NP_002438	277
TEK	TEK	NM_000459	2603-3433	160	149-3523	NP_000450	278
	Tie-1	NM_005424	2579-3409	161	80-3496	NP_005415	279
TNFR	TNFR1	NM_001065	1323-	247	282-	NP_001056	280

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Family	Member	nt ACC. #	Catalytic Domain	SEQ ID NO:	ORF	prt ACC.#	SEQ ID NO:
			1598(DD)		1649		
	TNFR2	NM_001066	n/a	3	90-1475	NP_001057	281
VEGFR	VEGFR-1	NM_002019	2704-3702	157	250-4266	NP_002010	282
	VEGFR-2	NM_002253	2779-3792	248	304-4374	NP_002244	283
	VEGFR-3	NM_002020	2530-3525	158	22-3918	NP_002011	284

Table 4: PRIMERS FOR PCR CLONING.

5

SEQ ID NO	Primer	Sequence
4	CSFIR_F1	CTG CCA CTT CCC CAC CGA GG
5	DDR1_F1	GGG ATC AGG AGC TAT GGG ACC A
6	DDR2_F1	CTG AGA TGA TCC TGA TTC CCA GAA
7	EphA1_F1	GGA GCT ATG GAG CGG CGC TG
8	EphA2_F1	AGC GAG AAG CGC GGC ATG GA
9	EphA3_F1	CAC CAG CAA CAT GGA TTG TCA GC
10	EphA4_F1	CGA ACC ATG GCT GGG ATT TTC TA
11	EphA7_F1	ATA AAA CCT GCT CAT GCA CCA TG
12	EphB1_F1	GCG ATG GCC CTG GAT TAT CTA
13	EphB2_F1	CCC CGG GAA GCG CAG CCA
14	EphB3_F1	GCT CCT AGA GCT GCC ACG GC
15	EphB4_F1	GAT CCT ACC CGA GTG AGG CGG
16	CSFIR_R1	GGG CTC CTG CAG AGA TGG GTA
17	DDR1_R1	AGA GCC ATT GGG GAC ACA GGG A
18	DDR2_R1	AGC CTG ACT CCT CCT CCC CTG
19	EphA1_R1	AGC TCT GTC AGC AAG ACC CTG G
20	EphA2_R1	AGG TGG TGT CTG GGG CCA GGT C
21	EphA3_R1	GTC AGG CTT GAG GCT ACT GAT GG
22	EphA4_R1	AAC ATA GGA AGT GAG AGG GTT CAG G
23	EphA7_R1	ACT CCA TTG GGA TGC TCT GGT TC
24	EphB1_R1	AGC CCA TCA ATC CTT GCT GTG
25	EphB2_R1	GCG TGC CCG CAC CTG GAA GA
26	EphB3_R1	GCT GGT CAC TGT GGA GGC GA
27	EphB4_R1	GGT AGC TGG CTC CCC GCT TCA
28	CSFIR_R2	CCG AGG GTC TTA CCA AAC TGC
29	DDR1_R2	AAG CGG AGT CGA GAT CGA GGG A
30	DDR2_R2	GGG GAA CTC CTC CAC AGC CA
31	EphA1_R2	CGG GTA AAG TCC AAG GCT CCC
32	EphA2_R2	GAC ACA GGA TGG ATG GAT CTC GG
33	EphA3_R2	ATC AAT GGA TAT GTT GGT GGC ATC
34	EphA4_R2	AGG ATG CGT CAA TTT CTT TGG CA

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SEQ ID	Primer	Sequence
35	EphA7_R2	CTG CAC CAA TCA CAC GCT CAA
36	EphB1_R2	ATC AAT CTC CTT GGC AAA CTC C
37	EphB2_R2	GCC CAT GAT GGA GGC TTC GC
38	EphB3_R2	ACG CAG GAC ACG TCG ATC TCC
39	EphB4_R2	ACC TGC ACC AAT CAC CTC TTC AA
40	EphB6_F1	AGA GTG GCG GGC ATG GTG TG
41	EphB6_R1	GCG GAG CTG ATA GTC CAG GAT G
42	EphB6_R2	CCT GTC CCA ATG ACC TCC TCA A
43	EphA6_F1	GGA GAT GAA AGA CTC TCC ATT TCA AG
44	FGFR-1_F1	ATT CGG GAT GTG GAG CTG GA
45	FGFR-2_F1	AGG ACC GGG GAT TGG TAC CG
46	FGFR-3_F1	CAT GGG CGC CCC TGC CTG
47	FGFR-4_F1	AGA AGG AGA TGC GGC TGC TG
48	TNFR1 (p55)_F1	AGC TGT CTG GCA TGG GCC TCT C
49	TNFR2 (p75)_F1	ACC GGA CCC CGC CCG CAC
50	EphA6_R1	ATCT TAG ACC GAC AGA AAA TTT GGC
51	FGFR-1_R1	CAA GGG ACC ATC CTG CGT GC
52	FGFR-2_R1	AGG GGC TTG CCC AGT GTC AG
53	FGFR-3_R1	GCT CCC ATT TGG GGT CGG CA
54	FGFR-4_R1	CGG GGG AAC TCC CAT AGT GG
55	TNFR1 (p55)_R1	GGC GCA GCC TCA TCT GAG AAG A
56	TNFR2 (p75)_R1	CAC AGC CCA CAC CGG CCT GG
57	Flt3_F1	GGA GGC CAT GCC GGC GTT G
58	KIT-F1	CGC AGC TAC CGC GAT GAG AGG
59	MET_F1	CTC ATA ATG AAG GCC CCC GC
60	PDGFR-A_F1	AAG TTT CCC AGA GCT ATG GGG A
61	PDGFR-B_F1	AGC AGC AAG GAC ACC ATG CG
62	RON_F1	GGT CCC AGC TCG CCT CGA TG
63	TEK_F1	AGA TTT GGG GAA GCA TGG ACT C
64	Tie-1_F1	CGG CCT CTG GAG TAT GGT CTG
65	VEGFR-1_F1	CAT GGT CAG CTA CTG GGA CAC C
66	VEGFR-2_F1	AGG TGC AGG ATG CAG AGC AAG
67	VEGFR-3_F1	AGC GGC CGG AGA TGC AGC G
68	Flt3_R1	CTG CTC GAC ACC CAC TGT CCA
69	KIT-R1	GCA GAA GTC TTG CCC ACA TCG
70	MET_R1	CTT CGT GAT CTT CTT CCC AGT GA
71	PDGFR-A_R1	AGA TTC TTA GCC AGG CAT CGC A
72	PDGFR-B_R1	AGC GCA CCG ACA GTG GCC GA
73	RON_R1	GCA CGG GCT GCC CAC TGT CA
74	TEK_R1	CTG TCC GAG GTT CCA AAT AGT TGA
75	Tie-1_R1	CGT TCT CAC TGG GGT CCA CCA
76	VEGFR-1_R1	ATT ATT GCC ATG CGC TGA GTG A
77	VEGFR-2_R1	GCC GCT TGG ATA ACA AGG GTA
78	VEGFR-3_R1	AAC TCG GTC CAG GTG TCC AGG C
79	Flt3_R2	CTT GGA AAC TCC CAT TTG AGA TCA
80	KIT-R2	ACA ACC TTC CCG AAA GCT CCA
81	MET_R2	ACT ACA TGC TGC ACT GCC TGG A
82	PDGFR-A_R2	CCC GAC CAA GCA CTA GTC CAT C



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SEQ ID	NO	Primer	Sequence
	83	PDGFR-B_R2	CCA GAG CCG AGG GTG CGT CC
	84	RON_R2	CAG GTC ATT CAG GTT GGG AGG A
	85	TEK_R2	ATT TGA TGT CAT TCC AGT CAA GCA
	86	Tie-1_R2	AGC ACT GGG TAG CTC AGG GGC
	87	VEGFR-1_R2	AAC TCC CAC TTG CTG GCA TCA
	88	VEGFR-2_R2	AAT TCC CAT TTG CTG GCA TCA
	89	VEGFR-3_R2	ATT CCC ACT GGC TGG CAT CGT A

#### D. Cloning and sequencing of PCR products

PCR products were electrophoresed on a 1% agarose gel, and DNA from detectable bands was stained with Gelstar (BioWhitaker Molecular Application, Walkersville, MD). The DNA bands were extracted with the QiaQuick gel extraction kit (Qiagen, Valencia, CA), ligated into the pDrive UA-cloning vector (Qiagen), and transformed into *Escherichia coli*. Recombinant plasmids were selected on LB agar plates containing 100 µg/ml carbenicillin. For each transfection, 192 colonies were randomly picked and their cDNA insert sizes were determined by PCR with M13 forward and reverse vector primers. Representative clones from PCR products with distinguishable molecular masses as visualized by fluorescence imaging (Alpha Innotech, San Leandro, CA) were then sequenced from both directions with vector primers (M13 forward and reverse). All clones were sequenced entirely using custom primers for directed sequencing completion across gapped regions.

#### E. Sequence analysis

Computational analysis of alternative splicing was performed by alignment of each cDNA sequence to its respective genomic sequence using SIM4 (a computer program for analysis of splice variants). Only transcripts with canonical (e.g. GT-AG) donor-acceptor splicing sites were considered for analysis. Clones encoding CSR isoforms were studied further (see below, Table 5).

#### F. Targeted cloning and expression

Computational analysis of public EST databases identified potential splice variants with intron retention or insertion. Cloning of potential splice variants identified by EST database analysis were performed by RT-PCR using primers flanking the open reading frame as described above.

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Sequence-verified CSR isoform encoding cDNA molecules were and can be subcloned into a replication-deficient recombinant adenoviral vector under control of the CMV promoter, following the manufacturer's instruction (Invitrogen, Cat# K4930-00). The recombinant adenoviruses were produced using 293A cells (Invitrogen). Supernatants from the infected 293 cells were analyzed by immunoblotting using an appropriate antibody.

### G. Exemplary CSR Isoforms

Exemplary CSR isoforms, prepared using the methods described herein, are set forth below in Table 5. Nucleic acid molecules encoding CSR isoforms are provided and include those that contain sequences of nucleotides or ribonucleotides or nucleotide or ribonucleotide analogs as set forth in any of SEQ ID NOS: 92, 94, 96, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, and 225. The amino acid sequences of exemplary CSR isoform polypeptides are set forth in any of SEQ ID NOS: 91, 93, 95, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 182, 184, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, and 226.

TABLE 5 CSR Isoforms

Gene	ID	Type	Length	SEQ ID NOS
FGFR-4	SR002_A11	Intron fusion	72 aa	90-91
KIT	SR002_H01	Intron fusion	413 aa	92-93
TNFR2	SR003_H02	Intron fusion	155 aa	94-95
DDR1	SR005_A11	Exon deletion	286 aa	114-115
DDR1	SR005_A10	Exon deletion	243 aa	116-117
FGFR-1	SR001_E12	Exon deletions	228 aa	118-119
FGFR-4	SR002_A10	Intron fusion	446 aa	120-121
VEGFR-1	SR004_C05	Intron fusion	174 aa	122-123
VEGFR-3	SR007_E10	Exon short	227 aa	124-125
VEGFR-3	SR007_F05	Exon deletion	295 aa	126-127
RON	SR004_C11	Intron fusion	495 aa	128-129
TEK	SR007_G02	Intron fusion, exon shorten	367 aa	130-131
TEK	SR007_H03	Exon deletion, Intron fusion	468 aa	132-133

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Gene	ID	Type	Length	SEQ ID NOS
Tie-1	SR006 A04	Intron fusion	251 aa	134-135
Tie-1	SR006 B07	Intron fusion	379 aa	136-137
Tie-1	SR006 B06	Intron fusion	161 aa	138-139
Tie-1	SR006 B12	Intron fusion	414 aa	140-141
Tie-1	SR006 B10	Exon deletion	317 aa	142-143
CSF1R	SR005 A06	Exon deletion	306 aa	144-145
PDGFR-B	SR007 C09	Exon shorten (4 bp)	336 aa	146-147
EphA1	SR004 G03	Intron fusion	474 aa	148-149
EphA1	SR004 G07	Intron fusion, exon deletion	311 aa	150-151
EphA1	SR004 H03	Intron fusion	490 aa	152-153
EphB1	SR005 D06	Exon shorten	242 aa	154-155
EphA2	SR016 E12	Intron fusion	497 aa	167-168
EphB4	SR012 C08	Exon deletion	306 aa	169-170
EphB4	SR012 D11	Exon shorten	516 aa	171-172
EphB4	SR012 E11	Exon shorted	414 aa	173-174
FGFR-1	SR022 C02	Exon deletion, intron fusion	320 aa	175-176
FGFR-2	SR022 C10	Intron fusion	266 aa	177-178
FGFR-2	SR022 C11	Intron fusion	317 aa	179-180
FGFR-2	SR022 D04	Exon deletion, intron fusion	281 aa	181-182
FGFR-2	SR022 D06	Intron fusion	396 aa	183-184
MET	SR020 C10	Intron fusion	413 aa	185-186
MET	SR020 C12	Intron fusion	468 aa	187-188
MET	SR020 D04	Intron fusion	518 aa	189-190
MET	SR020 D07	Intron fusion	596 aa	191-192
MET	SR020 D11	Intron fusion	408 aa	193-194
MET	SR020 E11	Intron fusion	621 aa	195-196
MET	SR020 F08	Intron fusion	664 aa	197-198
MET	SR020 F11	Intron fusion	719 aa	199-200
MET	SR020 F12	Intron fusion	697 aa	201-202
MET	SR020 G03	Exon shorten, intron fusion	691 aa	203-204
MET	SR020 G07	Intron fusion	661 aa	205-206
MET	SR020 H03	Intron fusion	755 aa	207-208
MET	SR020 H06	Intron fusion	823 aa	209-210
MET	SR020 H07	Intron fusion	877 aa	211-212
MET	SR020 H08	Exon deletion, intron fusion	764 aa	213-214
RON	SR014 C01	Intron fusion	541 aa	215-216
RON	SR014 C09	Intron fusion	908 aa	217-218
RON	SR014 E12	Intron fusion	647 aa	219-220
Tie-1	SR016 G03	Intron fusion	751 aa	221-222
VEGFR-1	SR01 C02	Intron fusion	541 aa	100
VEGFR-2	SR015 F01	Exon shorten	712 aa	223-224

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Gene	ID	Type	Length	SEQ ID NOS
VEGFR-3	SR015_G09	Intron fusion	765 aa	225-226

**Example 2****CSR Isoform expression Assays****A. Analysis of mRNA expression**

5 Expression of the cloned CSR isoforms were determined by RT-PCR (or quantitative PCR) in various tissues including: brain, heart, kidney, placenta, prostate, spleen, spinal cord, trachea, testis, uterus, fetal brain, fetal liver, adrenal gland, liver, lung, small intestine, salivary gland, skeletal muscle, thymus, thyroid and a variety of tumor tissues including: breast, colon, kidney, lung, ovary, stomach, uterus, MDA435  
 10 and HEPG2. PCR primers (such as set forth in Example 1, Table 4) were selected within the exclusive regions of retained introns or alternative exons, such that only the soluble receptor-specific signals were amplified. Each PCR reaction was performed with 2 cycle numbers (e.g. 32 versus 38 cycles) for the purpose of getting semi-quantitative results. Expression of each cloned CSR isoform was compared to the  
 15 expression of the corresponding wildtype membrane receptor.

EphA2 (GenBank No. NM\_004431 or SEQ ID NO: 229) mRNA is highly expressed in brain, heart, kidney, placenta, prostate, spleen, spinal cord, trachea, testis, uterus, fetal brain, fetal liver, adrenal gland, liver, lung, small intestine, salivary gland, skeletal muscle, thymus, and thyroid as well as expressed in the following  
 20 tumor tissues: breast, colon, kidney, lung, ovary, stomach, uterus, MDA435 and HEPG2. Soluble EphA2 (SEQ ID NO: 167) mRNA is highly expressed in the trachea, lung, small intestine, and salivary gland and to a lesser extent expressed in kidney, placenta, fetal brain, fetal liver, adrenal gland, skeletal muscle, thymus, brain, heart, spleen, spinal cord, uterus, and liver as well as highly expressed in stomach  
 25 tumor and to a lesser extent in colon, kidney, lung, ovary, uterus, MDA435 and HEPG2 tumor tissues.

FGFR-4 (GenBank No. NM\_002011 set forth as SEQ ID NO: 2) mRNA is expressed in a variety of human tissues, including brain, heart, kidney, placenta, prostate, spleen, spinal cord, trachea, testis, uterus, fetal brain, fetal liver, adrenal  
 30 gland, liver, lung, small intestine, salivary gland, skeletal muscle, thymus, and

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thyroid. FGFR-4 mRNA also is expressed in the following tumor tissues: breast, colon, kidney, lung, ovary, stomach, uterus, and HEPG2. Soluble FGFR-4 (SEQ ID NO: 120) mRNA is highly expressed in the kidney, spleen, testis, fetal brain, fetal liver, adrenal gland, liver, lung, small intestine and to a lesser extent expressed in  
5 brain, heart, placenta, prostate, spinal cord, trachea, uterus, skeletal muscle, thymus and thyroid. Soluble FGFR-4 (SEQ ID NO: 120) mRNA also is highly expressed in kidney and stomach tumor tissue and to a lesser extent in breast, colon, lung, ovary, and HEPG2 tumor tissues.

RON (GenBank No. NM\_002447 set forth as SEQ ID NO:159) mRNA is  
10 highly expressed in trachea, testis, fetal brain, lung, small intestine, and thymus as well as being expressed in salivary gland, kidney, placenta, heart, prostate, thyroid and to a lesser extent brain, spleen, spinal cord, uterus, fetal liver, adrenal gland, liver, and skeletal muscle. RON mRNA also is expressed in the following tumor tissues: breast, colon, lung, ovary, stomach, HEPG2 and to a lesser extent in kidney and  
15 uterus tumor tissue. Soluble RON (SEQ ID NO:128) mRNA is highly expressed in colon and stomach tumor tissues. Soluble RON (SEQ ID NO:128) mRNA is expressed to a lesser extent in trachea, small intestine and thymus as well as in breast, lung, and ovary tumor tissues. Soluble RON (SEQ ID NO:219) mRNA is highly expressed in prostate, trachea, fetal brain, lung, small intestine, thymus as well as  
20 breast, colon, lung, ovary, and stomach tumor tissues. Soluble RON (SEQ ID NO:219) mRNA also is expressed to a lesser extent in brain, heart, kidney, placenta, spleen, spinal cord, testis, uterus, fetal liver, adrenal gland, liver, salivary gland, skeletal muscle, thyroid as well as kidney, uterus, MDA435 and HEPG2 tumor tissues. Soluble RON (SEQ ID NO:217) mRNA is highly expressed in trachea, lung,  
25 small intestine, thymus as well as breast and colon tumor tissues. Soluble RON (SEQ ID NO:217) mRNA is expressed to a lesser extent in brain, heart, kidney, placenta, prostate, spleen, testis, uterus, fetal brain, salivary gland, thyroid as well as lung, ovary, and stomach tumor tissues.

TEK (GenBank No. NM\_000459 set forth as SEQ ID NO:160) mRNA is  
30 highly expressed in heart, kidney, placenta, spleen, lung as well as colon, kidney, lung, and ovary tumor tissues. TEK mRNA also is expressed to a lesser extent in

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brain, prostate, spinal cord, trachea, testis, uterus, fetal brain, fetal liver, adrenal gland, liver, small intestine, skeletal muscle, thymus, thyroid as well as breast and stomach tumor tissues. Soluble TEK (SEQ ID NO:132) mRNA has low level expression in heart and kidney, as well as colon tumor tissues.

5           VEGFR-1 (GenBank No. NM\_002019 set forth as SEQ ID NO:157) mRNA is highly expressed in brain, heart, kidney, placenta, prostate, spleen, spinal cord, testis, uterus, fetal brain, fetal liver, adrenal gland, lung, small intestine, skeletal muscle and to a lesser extent in trachea, liver, salivary gland, thymus and thyroid. VEGFR-1 mRNA also is highly expressed in colon, kidney, lung and ovary tumor  
10 tissues and to a lesser extent expressed in breast and stomach tumor tissues. Soluble VEGFR-1 (SEQ ID NO:100) mRNA has low level expression in stomach tumor tissues.

          VEGFR-3 (GenBank No. NM\_002020 set forth as SEQ ID NO:158) mRNA is highly expressed in heart, kidney, placenta, spleen, fetal brain, fetal liver, lung, small  
15 intestine as well as breast, colon, kidney, lung, ovary, stomach and uterus tumor tissues. VEGFR-3 (SEQ ID NO:158) mRNA is to a lesser extent expressed in brain, prostate, spinal cord, trachea, testis, uterus, adrenal gland, liver, salivary gland, skeletal muscle, thymus, thyroid. Soluble VEGFR-3 (SEQ ID NO:225) mRNA is highly expressed in placenta, adrenal gland, lung, small intestine as well as breast,  
20 kidney, lung tumor tissues. Soluble VEGFR-3 (SEQ ID NO:225) mRNA also is expressed to a lesser extent in brain, heart, kidney, prostate, spleen, spinal cord, trachea, testis, uterus, fetal brain, fetal liver, liver, salivary gland, skeletal muscle, thymus, and thyroid as well as colon, ovary, stomach, and uterus tumor tissues.

          In summary, expression of mRNA was detectable for all CSR isoforms, but in  
25 general was lower than that of the membrane receptor isoforms.

**B. Cell secretion of soluble receptors**

          Putative CSR isoforms were analyzed in cultured human cells to assess secreted isoforms. Splice variant cDNA molecules encoding candidate CSR isoforms were subcloned into a mammalian expression vector (pcDNA3.1MycHis vector  
30 (Invitrogen, Carlsbad, CA) fused in frame with the Myc-His tag at the C-terminus of the protein to facilitate their detection.

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Human embryonic kidney 293T cells were seeded at  $2 \times 10^6$  cells/well in a 6-well plate and maintained in Dulbecco's modified Eagle's medium and 10% fetal bovine serum (Invitrogen). Cells were transfected using LipofectAMINE 2000 (Invitrogen) following the manufacturer's instructions. On the day of transfection, 5  
5  $\mu$ g plasmid DNA was mixed with 15  $\mu$ l of LipofectAMINE 2000 in 0.5 ml of the serum-free DMEM. The mixture was incubated for 20 minutes at room temperature before it was added to the cells. Cells were incubated at 37°C in a CO<sub>2</sub> incubator for 48 hours. To study the transgene expression, the supernatants were collected and the cells were lysed in PBS buffer containing 0.2% of Triton X-100. Both the cell lysates  
10 and the supernatants were assayed for the transgene expression.

Ni-agarose NTA (Qiagen) was used for purifying His6-tagged proteins under native conditions following the manufacturer's instructions. Purified His6-tagged proteins were eluted and separated on SDS-polyacrylamide gels for immunoblotting using anti-Myc antibodies (both from Invitrogen). Antibodies were diluted 1:5000.

15 Expression of the secreted CSR isoforms was detected in cell lysates and conditioned media by Western blot using an anti-Myc antibody (Invitrogen) FGFR-4 (SEQ ID NO: 121), RON (SEQ ID NOS: 129, 216, 218, 220), VEGFR-2 (SEQ ID NO: 224), VEGFR-3 (SEQ ID NO: 127), EphA2 (SEQ ID NO:168), EphA1 (SEQ ID NOS: 153, 149), TEK (SEQ ID NOS: 131, 133), and Tie-1 (SEQ ID NO: 222) protein  
20 was detected in cell lysates and Tie-1 (SEQ ID NO: 222), VEGFR-2 (SEQ ID NO: 224), VEGFR-3 (SEQ ID NO: 127) and EphA2 (SEQ ID NO:168) protein was detected in conditioned medium.

### C. Receptor binding

Co-immunoprecipitation assays were performed to show binding of CSR  
25 isoforms and secreted isoforms to their respective membrane anchored full-length receptors (see, for example, *Jin et al. J Biol Chem* 2004, 279:1408 and *Jin et al. J Biol Chem* 2004, 279:14179). Human embryo kidney 293T cells were transiently transfected with the recombinant pcDNA 3.1(MycHis) plasmid expressing soluble VEGFR-3 (as described above). Forty-eight hours after transfection, conditioned  
30 medium was collected and binding of VEGF-D was assessed. Conditioned medium (100  $\mu$ l) from transfected 293T cells was incubated with VEGF-D (100 ng) in the

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presence or absence of 2 µg of soluble VEGFR-1-Fc or VEGFR-3-Fc (R&D Systems) for one hour. Protein complexes were immunoprecipitated with 0.2 µg/reaction of anti-VEGF-D antibodies (R&D Systems) and separated on a denaturing protein gel probed with anti-Myc antibody. The Western blot showed protein binding between  
5 sVEGF3-Myc and VEGF-D. Furthermore, 5x molar excess of a sVEGFR-3-Fc reduced binding whereas the presence of sVEGFR-1-Fc had little to no effect on binding.

#### **D. Proliferation Assays**

A biological activity of CSR isoforms was assessed by measuring their effect  
10 on cell proliferation. HUVEC cells (Clonitix) at passage 4 were seeded into DMEM/10%FBS at a density of 4,000 cells/well in a 96-well plate. Cells were treated with or without 0.5 nM of VEGF-A (R&D Systems) in the presence or absence of 2.5 nM of sVEGFR-1-Fc, 2.5 nM of sVEGFR-2-Fc, or 1.6 – 12.5 nM of the purified sVEGFR-2. The treated cells were cultured for 7 days in standard cell  
15 culture conditions. Cell proliferation was determined in triplicate samples using CyQuant Fluorescence Assay Kit (Invitrogen Catalog #C7026) according to manufacturer's instructions. 0.5 nM of VEGF-A induced HUVEC proliferation. sVEGFR-1-Fc (2.5 nM) and sVEGFR-2-Fc (2.5 nM) each inhibited VEGFA-induced HUVEC proliferation. Soluble VEGFR-2 (SEQ ID NO: 224) inhibited VEGF-A-  
20 induced HUVEC proliferation in a dose-dependent manner.

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims



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**CLAIMS:**

1. An isolated polypeptide, comprising at least one domain of an EphA receptor, wherein the polypeptide comprises an ephrin ligand binding domain and the polypeptide lacks one or more amino acids corresponding to the transmembrane domain of the EphA receptor whereby the membrane localization of the polypeptide is reduced or abolished compared to the EphA receptor.
2. The polypeptide of claim 1, wherein the EphA receptor is selected from the group consisting of EphA1, EphA2, EphA3, EphA4, EphA5, EphA6, EphA7, and EphA8.
3. The polypeptide of claim 2, wherein the EphA receptor comprises a sequence of amino acids set forth in any of SEQ ID NO: 253 – 260 or is an allelic variant thereof.
4. The polypeptide of claim 3, wherein the allelic variant comprises one or more of the allelic variations set forth in any one of SEQ ID NOS: 289-293.
5. A polypeptide of any of claims 1-4, wherein the polypeptide lacks all or part of a protein kinase domain compared to the EphA receptor.
6. The polypeptide of any of claims 1-5, wherein the polypeptide lacks all or part of a Sterile Alpha Motif domain (SAM) compared to the EphA receptor.
7. A polypeptide of claim 1, comprising at least one domain of an EphA1 receptor as set forth in SEQ ID NO:253.
8. The polypeptide of claim 7 that comprises an intron-encoded sequence of amino acids, wherein the intron is from a gene encoding the EphA1 receptor.
9. The polypeptide of claim 7, wherein the polypeptide comprises at least one domain of the EphA1 receptor operatively linked to at least one amino acid encoded by an intron of a gene encoding the EphA1 receptor.
10. The polypeptide of any of claims 7-9, wherein the polypeptide lacks one or more amino acids of a protein kinase domain of the EphA1 receptor, whereby the kinase activity of the polypeptide is reduced or abolished compared to the EphA1 receptor.

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11. The polypeptide of claim 10, wherein the polypeptide has at least 80% sequence identity with a sequence of amino acids set forth in any of SEQ ID NOS: 149, 151 and 153.

12. The polypeptide of claim 11 that comprises the amino acid sequence  
5 set forth in any of SEQ ID NOS: 149, 151 and 153 or is an allelic variant thereof.

13. The polypeptide of claim 12, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NO: 289.

14. The polypeptide of any of claims 7-13, wherein the polypeptide contains the same number of amino acids as set forth in any of SEQ ID NOS: 149,  
10 151 and 153.

15. The polypeptide of claim 1, comprising at least one domain of an EphA2 receptor as set forth in SEQ ID NO: 254, wherein the polypeptide lacks one or more amino acids of a transmembrane domain and protein kinase domain compared to the EphA2 receptor, whereby the membrane localization and the protein kinase  
15 activity of the polypeptide are reduced or abolished compared to the EphA2 receptor.

16. The polypeptide of claim 15 that comprises an intron-encoded sequence of amino acids, wherein the intron is from a gene encoding an EphA2 receptor.

17. The polypeptide of claim 15, wherein the polypeptide comprises at  
20 least one domain of EphA2 receptor operatively linked to at least one amino acid encoded by an intron of a gene encoding an EphA2 receptor.

18. The polypeptide of any of claims 15-17, wherein the polypeptide lacks one or more amino acids of a fibronectin domain compared to the EphA2 receptor.

19. The polypeptide of claim 18, wherein the polypeptide has at least 80%  
25 sequence identity with a sequence of amino acids as set forth in SEQ ID NO: 168.

20. The polypeptide of claim 19 that comprises the amino acid sequence set forth in SEQ ID NO: 168 or an allelic variant thereof.

21. The polypeptide of claim 20, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NO: 290.

22. The polypeptide of any of claims 15-21, wherein the polypeptide  
30 contains the same number of amino acids as set forth in the SEQ ID NO: 168.

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23. An isolated polypeptide, comprising at least one domain of an EphB receptor, wherein the polypeptide lacks one or more amino acids of a transmembrane domain compared to the EphB receptor, whereby the membrane localization of the polypeptide is reduced or abolished compared to the EphB receptor.

5        24. The polypeptide of claim 23, wherein the EphB receptor is selected from the group consisting of EphB1, EphB2, EphB3, EphB4, EphB5, and EphB6.

25. The polypeptide of claim 24, wherein the EphB receptor comprises a sequence of amino acids as set forth in any one of SEQ ID NOS: 261-265 or an allelic variant thereof.

10       26. The polypeptide of claim 25, wherein the allelic variant comprises one or more of the allelic variations as set forth in any one of SEQ ID NOS: 294-298.

27. The polypeptide of any of claims 23-26, wherein the polypeptide lacks one or more amino acids of a protein kinase domain of the EphB receptor, whereby the protein kinase activity of the polypeptide is reduced or abolished compared to the  
15 EphB receptor.

28. The polypeptide of any of claims 23-27, wherein the polypeptide lacks one or more amino acids of a Sterile Alpha Motif domain (SAM) of the EphB receptor.

29. The polypeptide of any of claims 23-28, wherein the polypeptide  
20 comprises an ephrin ligand binding domain.

30. The polypeptide of any of claims 23-29, wherein the polypeptide lacks one or more amino acids of a fibronectin domain of the EphB receptor.

31. The polypeptide of any of claims 23-30, wherein the polypeptide comprises an intron-encoded sequence of amino acids, wherein the intron is from a  
25 gene encoding the EphB receptor.

32. The polypeptide of claim 31, wherein the polypeptide comprises at least one domain of the EphB receptor operatively linked to at least one amino acid encoded by an intron of a gene encoding the EphB receptor.

33. The polypeptide of any of claims 23-32, wherein the polypeptide has at  
30 least 80% sequence identity with a sequence of amino acids as set forth in any of SEQ ID NOS: 155, 170, 172 and 174.

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34. The polypeptide of claim 33 that comprises the amino acid sequence as set forth in any of SEQ ID NOS: 155, 170, 172 and 174 or an allelic variant thereof.

35. The polypeptide of claim 34, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NOS: 294 or 297.

5 36. The polypeptide of any of claims 23-35, wherein the polypeptide contains the same number of amino acids as set forth in any of SEQ ID NOS: 155, 170, 172 and 174.

37. An isolated polypeptide, comprising at least one domain of an FGFR-1, wherein the polypeptide comprises an immunoglobulin domain corresponding to amino acids 253 – 357 of FGFR-1 set forth in SEQ ID NO: 268 and lacks all of a transmembrane domain corresponding to amino acids 375 – 397 of the FGFR-1.

10 38. The polypeptide of claim 37 that comprises an intron-encoded sequence of amino acids, wherein the intron is from a gene encoding the FGFR-1.

39. The polypeptide of claim 37, wherein the polypeptide comprises at least one domain of FGFR-1 operatively linked to at least one amino acid encoded by an intron of a gene encoding FGFR-1.

40. The polypeptide of any of claims 37-39, wherein the polypeptide lacks one or more amino acids of a protein kinase domain of FGFR-1, whereby the protein kinase activity of the polypeptide is reduced or abolished compared to the FGFR-1.

20 41. The polypeptide of any of claims 37-40, wherein the polypeptide comprises one or more amino acids of an immunoglobulin domain corresponding to amino acids 156 – 246 of FGFR-1.

42. The polypeptide of any of claims 37-41, wherein the polypeptide has at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NOS: 119 or 176.

25 43. The polypeptide of claim 42 that comprises the amino acid sequence as set forth in any of SEQ ID NOS: 119 and 176 or an allelic variant thereof.

44. The polypeptide of claim 43, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NO: 300.

30 45. The polypeptide of any of claims 37-44, wherein the polypeptide contains the same number of amino acids as set forth in SEQ ID NOS: 119 or 176.

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46. An isolated polypeptide, comprising at least one domain of an fibroblast growth factor receptor-2 (FGFR-2), wherein:

FGFR-2 comprises the sequence of amino acids set forth in SEQ ID NO: 269;

the polypeptide lacks a transmembrane domain and a protein kinase domain  
5 compared to FGFR-2, whereby the membrane localization and protein kinase activity of the polypeptide is reduced or abolished compared to FGFR-2; and

the polypeptide has at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NOS: 178, 180, 182 and 184.

47. The polypeptide of claim 46 that comprises an intron-encoded  
10 sequence of amino acids, wherein the intron is from a gene encoding the FGFR-2.

48. The polypeptide of claim 46, wherein the polypeptide comprises at least one domain of FGFR-2 operatively linked to at least one amino acid encoded by an intron of a gene encoding the FGFR-2.

49. The polypeptide of any of claims 46-48, wherein the polypeptide lacks  
15 an immunoglobulin domain corresponding to amino acids 41-125 of the FGFR-2.

50. The polypeptide of any of claims 46-48 that comprises the amino acid sequence set forth in SEQ ID NOS: 178, 180, 182 or 184 or an allelic variant thereof.

51. The polypeptide of claim 50, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NO: 301.

20 52. The polypeptide of any of claims 46-51, wherein the polypeptide contains the same number of amino acids as set forth in any of SEQ ID NOS: 178, 180, 182 and 184.

53. An isolated polypeptide, comprising at least one domain of an FGFR-4, wherein the polypeptide comprises an immunoglobulin domain corresponding to  
25 amino acids 249 – 351 of the FGFR-4 set forth in SEQ ID NO: 271 and lacks a transmembrane domain and protein kinase domain of the FGFR-4, whereby the membrane localization and protein kinase activity of the polypeptide is reduced or abolished compared to FGFR-4.

54. The polypeptide of claim 53 that comprises an intron-encoded  
30 sequence of amino acids, wherein the intron is from a gene encoding the FGFR-4.

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55. The polypeptide of claim 53, wherein the polypeptide comprises at least one domain of FGFR-4 operatively linked to at least one amino acid encoded by an intron of a gene encoding the FGFR-4.

56. The polypeptide of any of claims 53-55, wherein the polypeptide has at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NO: 121.

57. The polypeptide of any of claims 53-56, that comprises the amino acid sequence set forth in SEQ ID NO: 121 or an allelic variant thereof.

58. The polypeptide of claim 57, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NO: 303.

59. The polypeptide of any of claims 53-58, wherein the polypeptide contains the same number of amino acids as set forth in SEQ ID NO: 121.

60. An isolated polypeptide, comprising at least one domain of a DDR1 as set forth in SEQ ID NO: 250; wherein the polypeptide lacks a transmembrane domain and a protein kinase domain compared to the DDR1, whereby the membrane localization and protein kinase activity of the polypeptide is reduced or abolished compared to DDR1, and the polypeptide has at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NOS: 115 or 117.

61. The polypeptide of claim 60 that comprises an intron-encoded sequence of amino acids, wherein the intron is from a gene encoding the DDR1.

62. The polypeptide of claim 61, wherein the polypeptide comprises at least one domain of DDR1 operatively linked to at least one amino acid encoded by an intron of a gene encoding the DDR1.

63. The polypeptide of any of claims 60-62, that comprises the amino acid sequence set forth in SEQ ID NOS: 115 or 117 or an allelic variant thereof.

64. The polypeptide of claim 63, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NO: 286.

65. The polypeptide of any of claims 60-64, wherein the polypeptide contains the same number of amino acids as set forth in SEQ ID NOS: 115 or 117.

66. An isolated polypeptide, comprising at least one domain of a MET receptor, wherein:

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the polypeptide comprises at least one domain of MET operatively linked to at least one amino acid encoded by an intron of a gene encoding MET; and

the polypeptide lacks a transmembrane domain, protein kinase domain and at least one additional domain compared to a MET receptor set forth in SEQ ID NO:

5 274, whereby the membrane localization and protein kinase activity of the polypeptide is reduced or abolished compared to the MET receptor.

67. The polypeptide of claim 66 that comprises an intron-encoded sequence of amino acids, wherein the intron is from a gene encoding MET.

68. The polypeptide of claim 66, wherein the polypeptide comprises at  
10 least one domain of MET operatively linked to at least one amino acid encoded by an intron of a gene encoding MET.

69. The polypeptide of any of claims 66-68, wherein the additional domain is selected from the group consisting of a Sema domain, a plexin domain and an IPT/TIG domain.

15 70. The polypeptide of any of claims 66-69, wherein the polypeptide has at least 80% sequence identity with a sequence of amino acids as set forth in any of SEQ ID NOS: 186, 188, 190, 192, 196, 198, 200, 202, 204, 206, 208 and 214.

71. The polypeptide of any of claims 66-70, that comprises the amino acid sequence set forth in any of SEQ ID NOS: 186, 188, 190, 192, 196, 198, 200, 202,  
20 204, 206, 208 and 214 or an allelic variant thereof.

72. The polypeptide of claim 71, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NO: 306.

73. The polypeptide of any of claims 66-72, wherein the polypeptide contains the same number of amino acids as set forth in any of SEQ ID NOS: 186,  
25 188, 190, 192, 196, 198, 200, 202, 204, 206, 208 and 214.

74. An isolated polypeptide, comprising at least one domain of a RON receptor, wherein:

the polypeptide comprises a plexin domain of the RON receptor as set forth in SEQ ID NO: 277; and

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the polypeptide lacks a transmembrane domain of the RON receptor, whereby the membrane localization of the polypeptide is reduced or abolished compared to the RON receptor.

75. The polypeptide of claim 74 that comprises an intron-encoded  
5 sequence of amino acids, wherein the intron is from a gene encoding the RON receptor.

76. The polypeptide of claim 74, wherein the polypeptide comprises at least one domain of RON operatively linked to at least one amino acid encoded by an intron of a gene encoding RON.

10 77. The polypeptide of any of claims 74-76, wherein the polypeptide lacks one or more amino acids of a protein kinase domain compared to the RON receptor as set forth in SEQ ID NO: 277, whereby the protein kinase activity of the polypeptide is reduced or abolished compared to the RON receptor.

78. The polypeptide of any of claims 74-77, wherein the polypeptide  
15 comprises one or more amino acids of at least one IPT/TIG domain of the RON receptor.

79. The polypeptide of any of claims 74-78, wherein the polypeptide has at least 80% sequence identity with a sequence of amino acids as set forth in any of SEQ ID NOS: 216, 218 and 220.

20 80. The polypeptide of any of claims 74-79, that comprises the amino acid sequence set forth in any of SEQ ID NOS: 216, 218 and 220 or an allelic variant thereof.

81. The polypeptide of claim 80, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NO: 308.

25 82. The polypeptide of any of claims 74-81, wherein the polypeptide contains the same number of amino acids as set forth in any of SEQ ID NOS: 216, 218 and 220.

83. An isolated polypeptide, comprising at least one domain of a TEK receptor as set forth in SEQ ID NO: 278, wherein:



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the polypeptide lacks a transmembrane domain, and a protein kinase domain whereby the membrane localization and protein kinase activity of the polypeptide are reduced or abolished compared to the TEK receptor; and

the polypeptide lacks one or more amino acids of at least one fibronectin domain compared to the TEK receptor.

84. The polypeptide of claim 83 that comprises an intron-encoded sequence of amino acids, wherein the intron is from a gene encoding the TEK receptor.

85. The polypeptide of claim 83, wherein the polypeptide comprises at least one domain of the TEK receptor operatively linked to at least one amino acid encoded by an intron of a gene encoding the TEK receptor.

86. The polypeptide of any of claims 83-85, wherein the fibronectin domain lacking in the polypeptide corresponds to amino acids 444 – 529, 543 – 626, or 639 – 724 of SEQ ID NO: 278.

87. The polypeptide of any of claims 83-86, wherein the polypeptide lacks one or more amino acids of the three fibronectin domains of the TEK receptor corresponding to amino acids 444 – 529, 543 – 626, and 639 – 724 of SEQ ID NO: 278.

88. The polypeptide of any of claims 83-87, wherein the polypeptide has at least 80% sequence identity with a sequence of amino acids as set forth in any of SEQ ID NOS: 131 and 133.

89. The polypeptide of any of claims 83-88, that comprises the amino acid sequence set forth in any of SEQ ID NOS: 131 and 133 or an allelic variant thereof.

90. The polypeptide of claim 89, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NO: 309.

91. The polypeptide of any of claims 83-90, wherein the polypeptide contains the same number of amino acids as set forth in any of SEQ ID NOS: 131 and 133.

92. An isolated polypeptide, comprising all or part of at least one domain of a Tie-1 receptor as set forth in SEQ ID NO: 279, wherein:

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the polypeptide lacks a transmembrane domain and a protein kinase domain compared to the Tie-1 receptor, whereby the membrane localization and protein kinase activity of the polypeptide are reduced or abolished compared to the Tie-1 receptor; and

5 the polypeptide comprises an amino acid sequence as set forth in any of SEQ ID NOS: 135, 137, 139, 141, 143 and 222 or an allelic variant thereof.

93. The polypeptide of claim 92, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NO: 310.

94. The polypeptide of any of claims 92 and 93, wherein the polypeptide  
10 contains the same number of amino acids as set forth in any of SEQ ID NOS: 135, 137, 139, 141, 143 and 222.

95. An isolated polypeptide, wherein:

the polypeptide comprises a sequence of amino acids that has at least 80% sequence identity with the sequence of amino acids as set forth in SEQ ID NO: 123;  
15 and

the polypeptide lacks a transmembrane domain and a protein kinase domain compared to the VEGFR-1 receptor set forth in SEQ ID NO: 282.

96. The polypeptide of claim 95, that comprises the amino acid sequence set forth in SEQ ID NO: 123 or an allelic variant thereof.

97. The polypeptide of any of claims 95-96, wherein the polypeptide  
20 contains the same number of amino acids as set forth in SEQ ID NO: 123.

98. An isolated polypeptide, comprising at least one domain of a VEGFR set forth in any of SEQ ID NOS: 283 and 284, wherein the polypeptide lacks one or more amino acids of a transmembrane domain of the VEGFR, whereby the membrane  
25 localization of the polypeptide is reduced or abolished compared to the VEGFR.

99. The polypeptide of claim 98 that comprises an intron-encoded sequence of amino acids, wherein the intron is from a gene encoding the VEGFR.

100. The polypeptide of claim 99, wherein the polypeptide comprises at least one domain of the VEGFR operatively linked to at least one amino acid encoded  
30 by an intron of a gene encoding the VEGFR.

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101. The polypeptide of any of claims 98-100, wherein the polypeptide lacks one or more amino acids of a protein kinase domain, whereby the protein kinase activity of the polypeptide is reduced or abolished compared to the VEGFR.

102. The polypeptide of any of claims 98-101, wherein the polypeptide  
5 lacks one or more amino acids of an immunoglobulin domain compared to the VEGFR.

103. The polypeptide of claim 102, wherein the polypeptide has at least 80% sequence identity with a sequence of amino acids as set forth in any of SEQ ID NOS: 125, 127, 224 and 226.

104. The polypeptide of any of claims 99-103, that comprises the amino  
10 acid sequence set forth in any of SEQ ID NOS: 125, 127, 224 and 226 or an allelic variant thereof.

105. The polypeptide of claim 104, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NOS: 313 or  
15 314.

106. The polypeptide of any of claims 99-105, wherein the polypeptide contains the same number of amino acids as set forth in any of SEQ ID NOS: 125, 127, 224 and 226.

107. An isolated polypeptide, comprising at least one domain of a PDGFR-B as set forth in SEQ ID NO: 276, wherein the polypeptide lacks one or more amino  
20 acids of a transmembrane domain of the PDGFR-B, whereby the membrane localization of the polypeptide is reduced or abolished compared to the PDGFR-B.

108. The polypeptide of claim 107, that comprises an intron-encoded sequence of amino acids, wherein the intron is from a gene encoding the PDGFR-B.

109. The polypeptide of claim 107, wherein the polypeptide comprises at  
25 least one domain of PDGFR-B operatively linked to at least one amino acid encoded by an intron of a gene encoding the PDGFR-B.

110. The polypeptide of any of claims 107-109, wherein the polypeptide lacks one or more amino acids of a protein kinase domain of the PDGFR-B, whereby  
30 the protein kinase activity of the polypeptide is reduced or abolished compared to the PDGFR-B.

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111. The polypeptide of any of claims 107-110, wherein the polypeptide comprises one or more amino acids of an immunoglobulin domain of the PDGFR-B.

112. The polypeptide of any of claims 107-111, wherein the polypeptide has at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NO: 147.

113. The polypeptide of any of claims 107-112, that comprises the amino acid sequence set forth in SEQ ID NO: 147 or an allelic variant thereof.

114. The polypeptide of claim 113, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NO: 307.

115. The polypeptide of any of claims 107-114, wherein the polypeptide contains the same number of amino acids as set forth in SEQ ID NO: 147.

116. An isolated polypeptide, comprising at least one domain of a CSF1R as set forth in SEQ ID NO: 249, wherein the polypeptide lacks one or more amino acids of a transmembrane domain of the CSF1R, whereby the membrane localization of the polypeptide is reduced or abolished compared to the CSF1R.

117. The polypeptide of claim 116, that comprises an intron-encoded sequence of amino acids, wherein the intron is from a gene encoding the CSF1R.

118. The polypeptide of claim 117, wherein the polypeptide comprises at least one domain of CSF1R operatively linked to at least one amino acid encoded by an intron of a gene encoding the CSF1R.

119. The polypeptide of any of claims 116-118, wherein the polypeptide lacks one or more amino acids of a protein kinase domain of the CSF1R, whereby the protein kinase activity of the polypeptide is reduced or abolished compared to the CSF1R.

120. The polypeptide of any of claims 116-119, wherein the polypeptide comprises one or more amino acids of an immunoglobulin domain of the CSF1R.

121. The polypeptide of any of claims 116-120, wherein the polypeptide has at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NO: 145.

122. The polypeptide of any of claims 116-121, that comprises the amino acid sequence set forth in SEQ ID NO: 145 or an allelic variant thereof.

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123. The polypeptide of claim 122, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NO: 285.

124. The polypeptide of any of claims 116-123, wherein the polypeptide contains the same number of amino acids as set forth in SEQ ID NO: 145.

5 125. An isolated polypeptide, comprising at least one domain of a KIT receptor as set forth in SEQ ID NO:273 and lacks one or more amino acids of a transmembrane domain and a protein kinase domain of the KIT receptor, whereby the membrane localization and protein kinase activity of the polypeptide are reduced or abolished compared to the KIT receptor.

10 126. The polypeptide of claim 125, that comprises an intron-encoded sequence of amino acids, wherein the intron is from a gene encoding the KIT receptor.

127. The polypeptide of claim 125, wherein the polypeptide comprises at least one domain of KIT receptor operatively linked to at least one amino acid encoded by an intron of a gene encoding KIT receptor.

128. The polypeptide of any of claims 125-127, wherein the polypeptide comprises at least one immunoglobulin domain of the KIT receptor.

129. The polypeptide of any of claims 125-128, wherein the polypeptide has at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NO: 93.

130. The polypeptide of any of claims 125-129, that comprises the amino acid sequence set forth in SEQ ID NO: 93 or an allelic variant thereof.

131. The polypeptide of claim 130, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NO: 305.

25 132. The polypeptide of any of claims 125-131, wherein the polypeptide contains the same number of amino acids as set forth in SEQ ID NO: 93.

133. An isolated polypeptide, comprising at least one cysteine rich c6 domain of a TNFR as set forth in SEQ ID NOS: 280 or 281 and lacks all of the transmembrane domain of the TNFR, whereby the membrane localization of the polypeptide is reduced or abolished compared to the TNFR.

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134. The polypeptide of claim 133, that comprises an intron-encoded sequence of amino acids, wherein the intron is from a gene encoding the TNFR.

135. The polypeptide of claim 133, wherein the polypeptide comprises at least one domain of TNFR operatively linked to at least one amino acid encoded by an intron of a gene encoding the TNFR.

136. The polypeptide of any of claims 133-135, wherein the polypeptide comprises at least two cysteine rich c6 domains of the TNFR.

137. The polypeptide of any of claims 133-136, wherein the polypeptide has at least 80% sequence identity with a sequence of amino acids set forth in SEQ ID NO: 95.

138. The polypeptide of any of claims 133-137, that comprises the amino acid sequence set forth in SEQ ID NO: 95 or an allelic variant thereof.

139. The polypeptide of claim 138, wherein the allelic variant comprises one or more amino acids of the allelic variations as set forth in SEQ ID NO: 312.

140. The polypeptide of any of claims 133-139, wherein the polypeptide contains the same number of amino acids as set forth in SEQ ID NO: 95.

141. The polypeptide of any of claims 1-140, wherein the polypeptide modulates a biological function of a cell surface receptor.

142. The polypeptide of claim 141, wherein the polypeptide modulates a biological function of the cognate receptor.

143. The polypeptide of claim 141 or claim 142, wherein the activity modulated by the polypeptide is one or more of: dimerization, homodimerization, heterodimerization, trimerization, kinase activity, receptor-associated kinase activity, receptor-associated protease activity, autophosphorylation of the cell surface receptor, transphosphorylation of the cell surface receptor, phosphorylation of a signal transduction molecule, ligand binding, competition with the cell surface receptor for ligand binding, signal transduction, interaction with a signal transduction molecule, induction of apoptosis, membrane association and membrane localization.

144. A pharmaceutical composition, comprising a polypeptide of any of claims 1-143.

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145. The composition of claim 144, comprising an amount of the polypeptide effective for modulating an activity of a cell surface receptor.

146. The composition of claim 145, wherein the polypeptide modulates a biological function of the cognate receptor.

5 147. The composition of claim 145 or claim 146, wherein the activity modulated by the polypeptide is one or more of: dimerization, homodimerization, heterodimerization, trimerization, kinase activity, receptor-associated kinase activity, receptor-associated protease activity, autophosphorylation of the cell surface receptor, transphosphorylation of the cell surface receptor, phosphorylation of a signal  
10 transduction molecule, ligand binding, competition with the cell surface receptor for ligand binding, signal transduction, interaction with a signal transduction molecule, induction of apoptosis, membrane association and membrane localization.

148. The composition of any one of claims 145-147, wherein modulation is an inhibition of activity.

15 149. The composition of any one of claims 145-148, wherein the polypeptide of the composition complexes with a receptor tyrosine kinase or a tumor necrosis factor receptor.

150. A nucleic acid molecule, comprising a sequence of nucleic acids encoding a polypeptide of any of claims 1-143.

20 151. The nucleic acid molecule of claim 150, comprising an intron and an exon, wherein:

the intron contains a stop codon;

the nucleic acid molecule encodes an open reading frame that spans an exon intron junction; and

25 the open reading frame terminates at the stop codon in the intron.

152. The nucleic acid molecule of claim 151, wherein the intron encodes one or more amino acids of the encoded polypeptide.

153. The nucleic acid molecule of claim 151 or claim 152, wherein the stop codon is the first codon in the intron.

30 154. An isolated nucleic acid molecule, comprising the sequence of nucleic acids set forth in any of SEQ ID NOS: 90, 92, 94, 114, 116, 118, 120, 122, 124, 126,

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128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223 and 225 or an allelic variant thereof.

155. A vector, comprising the nucleic acid molecule of any of claims 150-  
5 154.

156. A cell, comprising the vector of claim 155.

157. A method of treating a disease or condition comprising, administering  
a pharmaceutical composition of any of claims 144-149.

158. The method of claim 157, wherein the disease or condition is selected  
10 from the group consisting of cancers, inflammatory diseases, infectious diseases  
angiogenesis-related conditions (conditions involving angiogenesis), cell  
proliferation-related conditions, conditions involving hyperproliferation of cells,  
immune disorders and neurodegenerative diseases.

159. The method of claim 157, wherein the disease or condition is selected  
15 from the group consisting of rheumatoid arthritis, multiple sclerosis, posterior  
intraocular inflammation, uveitic disorders, ocular surface inflammatory disorders,  
neovascular disease, proliferative vitreoretinopathy, atherosclerosis, rheumatoid  
arthritis, hemangioma, diabetes mellitus, inflammatory bowel disease, psoriasis,  
Alzheimer's disease, lupus, vascular stenosis, restenosis, inflammatory joint disease,  
20 atherosclerosis, urinary obstructive syndromes, and asthma.

160. The method of claim 157, wherein the disease or condition is selected  
from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, leukemia,  
lymphoid malignancies, squamous cell cancer, small-cell lung cancer, non-small cell  
lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of  
25 the peritoneum, hepatocellular cancer, gastric cancer, stomach cancer, gastrointestinal  
cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer,  
bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal  
cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney/renal  
cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal  
30 carcinoma, penile carcinoma, and head and neck cancer.



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161. The method of claim 157, wherein the disease or condition includes infection by a virus or a parasite.

162. The method of claim 161, wherein the virus is selected from the group consisting of Myxoma virus, Vaccinia virus, Tanapox virus, Epstein-Barr virus,  
5 Herpes simplex virus, Cytomegalovirus, Herpesvirus saimiri, Hepatitis B virus, African swine fever virus, Parovirus, Human Immune deficiency virus (HIV), Hepatitis C virus, Influenza virus, Respiratory syncytial virus, Measles virus, Vesicular stomatitis virus, Dengue virus and Ebola virus.

163. The method of claim 157, wherein the pharmaceutical composition  
10 contains a polypeptide that inhibits angiogenesis, cell proliferation, cell migration, viral entry, viral infection, tumor cell growth or tumor cell metastasis.

164. An isolated polypeptide comprising the sequence of any one of SEQ ID NOS: 91, 93, 95, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139,  
141, 143, 145, 147, 149, 151, 153, 155, 168, 170, 172, 174, 176, 178, 180, 182, 184,  
15 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224 and 226.

165. An isolated polypeptide consisting essentially of the sequence of any one of SEQ ID NOS: 91, 93, 95, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133,  
135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 168, 170, 172, 174, 176, 178,  
20 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224 and 226.

166. An isolated polypeptide, comprising a sequence of amino acids that has at least 80% sequence identity with a sequence of amino acids set forth in any of SEQ ID NOS: 91, 93, 95, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137,  
25 139, 141, 143, 145, 147, 149, 151, 153 or 155 or allelic variations thereof, wherein:

sequence identity is compared along the full length of each SEQ ID to the full length sequence of the isolated polypeptide;

each of SEQ ID NOS: 91, 93, 95, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153 and 155 is a cell surface  
30 receptor isoform.

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167. An isolated polypeptide, comprising the sequence of amino acids set forth in any of SEQ ID NOS: 91, 93, 95, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153 or 155.

168. The isolated polypeptide of claim 166, wherein the polypeptide  
5 contains the same number of amino acids as set forth in the SEQ ID to which it has identity.

169. The isolated polypeptide of claim 166, wherein the polypeptide occurs in a mammal.

170. The isolated polypeptide of claim 169, wherein the mammal is a  
10 rodent, a primate or a human.

171. An isolated polypeptide, comprising at least one domain of a cell surface receptor operatively linked to at least one amino acid encoded by an intron of a gene encoding the cell surface receptor;

wherein the cell surface receptor is selected from the group consisting of  
15 DDR1, KIT, FGFR-1, FGFR-4, TNFR2, VEGFR-1, VEGFR-3, RON, TEK, Tie-1, CSF1R, PDGFR-B, EphA1, and EphB1; or

wherein the polypeptide comprises a sequence of amino acids selected from the group consisting of SEQ ID NOS: 91, 93, 95, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153 and 155.

20 172. An isolated polypeptide, comprising a shortened cell surface receptor lacking at least all or part of a transmembrane domain, wherein:

the polypeptide is not membrane localized;

the polypeptide modulates an activity of the cell surface receptor;

the cell surface receptor is selected from the group consisting of DDR1, KIT,  
25 FGFR-1, FGFR-4, TNFR2, VEGFR-1, VEGFR-3, RON, TEK, Tie-1, CSF1R, PDGFR-B, EphA1, and EphB1, or the isolated polypeptide has at least 80% sequence identity with a sequence of amino acids set forth in any of SEQ ID NOS: 91, 93, 95, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153 or 155; and

30 sequence identity is compared along the full length of each SEQ ID to the sequence of the full length of the isolated polypeptide.

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173. The isolated polypeptide of claim 172, wherein the cell surface receptor further lacks a cell surface receptor cytoplasmic domain.

174. An isolated polypeptide, comprising an intron-encoded sequence of amino acids, wherein:

5 the intron is from a cell surface receptor gene selected from the group consisting of KIT, FGFR-4, TNFR2, VEGFR-1, RON, TEK, Tie-1, and EphA1; or the intron-encoded sequence of any of SEQ ID NOS: 91, 93, 95, 121, 123, 129, 131, 133, 135, 137, 139, 141, 149, 151 and 153; and the polypeptide lacks a cell surface receptor cytoplasmic domain.

10 175. The polypeptide of claim 174, wherein the polypeptide further lacks a transmembrane domain.

176. The isolated polypeptide of claim 174 or claim 175, wherein the isolated polypeptide modulates a biological function of a cell surface receptor.

15 177. The isolated polypeptide of any of claims 166-176, wherein the polypeptide comprises a TNFR isoform and wherein the TNFR is selected from the group consisting of TNFR1, TNFR2, TNFR $\alpha$ , the low-affinity nerve growth factor receptor, Fas antigen, CD40, CD27, CD30, 4-1BB, OX40, DR3, DR4, DR5, and herpesvirus entry mediator (HVEM).

20 178. A pharmaceutical composition, comprising a polypeptide of any of claims 171-177.

179. The composition of claim 178, comprising an amount of the polypeptide effective for modulating an activity of a cell surface receptor.

25 180. The composition of claim 179, wherein the activity of the cell surface receptor modulated by the polypeptide is one or more of dimerization, homodimerization, heterodimerization, trimerization, kinase activity, receptor-associated kinase activity, receptor-associated protease activity, autophosphorylation of the cell surface receptor, transphosphorylation of the cell surface receptor, phosphorylation of a signal transduction molecule, ligand binding, competition with the cell surface receptor for ligand binding, signal transduction, interaction with a  
30 signal transduction molecule, induction of apoptosis, membrane association and membrane localization.

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181. The composition of claim 179 or claim 180, wherein modulation is an inhibition of activity.

182. The composition of claim 179 or claim 180, wherein the polypeptide of the composition complexes with a receptor tyrosine kinase or a tumor necrosis factor  
5 receptor.

183. A nucleic acid molecule encoding a polypeptide of any of claims 166-177.

184. The nucleic acid molecule of claim 183, comprising an intron and an exon, wherein:

10 the intron contains a stop codon;  
the nucleic acid molecule encodes an open reading frame that spans an exon intron junction; and  
the open reading frame terminates at the stop codon in the intron.

185. The nucleic acid molecule of claim 184, wherein the intron encodes  
15 one or more amino acids of the encoded polypeptide.

186. The nucleic acid molecule of claim 184 or claim 185, wherein the stop codon is the first codon in the intron.

187. An isolated nucleic acid molecule, comprising a sequence of nucleotides that has at least 90% sequence identity with a sequence of nucleotides set  
20 forth in any of SEQ ID NOS: 90, 92, 94, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152 or 154 and allelic variations thereof, wherein:

sequence identity is compared along the full length of each SEQ ID to the full length sequence of the isolated nucleic acid molecule; and  
25 each of SEQ ID NOS: 90, 92, 94, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152 and 154 is a cell surface receptor isoform.

188. An isolated nucleic acid molecule comprising SEQ ID NOS: 90, 92, 94, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144,  
30 146, 148, 150, 152 or 154.

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189. A vector, comprising the nucleic acid molecule of any of claims 183-188.

190. A cell, comprising the vector of claim 189.

191. A method of treating a disease or condition comprising, administering  
5 a pharmaceutical composition of any of claims 178-182.

192. The method of claim 191, wherein the disease or condition is selected from the group consisting of cancers, inflammatory diseases, infectious diseases, angiogenesis-related conditions, cell proliferation-related conditions, immune disorders and neurodegenerative diseases.

10 193. The method of claim 191, wherein the disease or condition is selected from the group consisting of rheumatoid arthritis, multiple sclerosis, posterior intraocular inflammation, uveitic disorders, ocular surface inflammatory disorders, neovascular disease, proliferative vitreoretinopathy, atherosclerosis, rheumatoid arthritis, hemangioma, diabetes mellitus, inflammatory bowel disease, psoriasis,  
15 Alzheimer's disease, lupus, vascular stenosis, restenosis, inflammatory joint disease, atherosclerosis, urinary obstructive syndromes, and asthma.

194. The method of claim 191, wherein the disease or condition is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, leukemia, lymphoid malignancies, squamous cell cancer, small-cell lung cancer, non-small cell  
20 lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric cancer, stomach cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney/renal  
25 cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, and head and neck cancer.

195. The method of claim 191, wherein the disease or condition is infection by a virus or a parasite.

196. The method of claim 195, wherein the virus is selected from the group  
30 consisting of Myxoma virus, Vaccinia virus, Tanapox virus, Epstein-Barr virus, Herpes simplex virus, Cytomegalovirus, Herpesvirus saimiri, Hepatitis B virus,

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African swine fever virus, Parovirus, Human Immune deficiency virus (HIV), Hepatitis C virus, Influenza virus, Respiratory syncytial virus, Measles virus, Vesicular stomatitis virus, Dengue virus and Ebola virus.

197. The method of claim 191, wherein the pharmaceutical composition  
5 contains a polypeptide that inhibits angiogenesis, cell proliferation, cell migration, viral entry, viral infection, tumor cell growth or tumor cell metastasis.

198. A method of regulating development and/or disease states, comprising contacting cells or tissues *in vitro* or *in vivo* with a cell surface receptor isoform (CSR) that lacks one or more domains or activities of the CSR, wherein the CSR is  
10 involved in angiogenesis or development

199. The method of claim 198, wherein the CSR is an intron fusion protein.

200. A chimeric polypeptide, comprising a portion of one cell surface receptor (CSR) isoform and a portion of a second, different CSR isoform, wherein:  
the chimeric isoform modulates the activity of one or more tyrosine kinase  
15 receptors; and  
each portion contains at least 4, 5, 6, 7, 8, 10, 12, 15, or more amino acid residues.

201. The polypeptide of claim 200, wherein the first and second cell surface receptor isoforms comprise a polypeptide selected from polypeptides of any of claims  
20 1-143 and 165-177 or is a herstatin polypeptide.

202. The polypeptide of claim 200 or claim 201, wherein the first portion comprises all or part of an extracellular domain of a cell surface receptor; and the second portion comprises an intron from an intron fusion protein.

203. The polypeptide of claim 201, wherein the intron-encoded portion is a  
25 herstatin intron-encoded portion.

204. The polypeptide of claim 203, wherein the intron is set forth in any of SEQ ID NOS: 320-359.

205. A conjugate, comprising: a first portion linked directly or via a linker to an intron-encoded portion of an intron fusion polypeptide, wherein the resulting  
30 polypeptide modulates the activity of a cell surface receptor.

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206. The conjugate of claim 205, wherein the first portion is all or part of an extracellular domain of any cell surface receptor (CSR).

207. The conjugate of claim 206, wherein the CSR is a receptor tyrosine kinase.

5        208. The conjugate of any of claims 205-207 or the chimeric polypeptides any of claims 200-204, wherein the first and second portions are from a polypeptide set forth in any of claims 1-143 and 164-177 or are from a herstatin, wherein if a portion is from herstatin the first or second portions are linked via a linker or on portion is not from a herstatin.

10       209. The conjugate or chimera of any of claims 200-207, wherein the first portion is from serum albumin.

210. The conjugate or chimera of any of claims 200-209, comprising an intron-encoded portion that is a herstatin intron.

211. A polypeptide comprising:  
15       an N-terminal portion from a cell surface receptor other than HER-2 ; and an intron, wherein:

the polypeptide lacks at least all or part of a transmembrane domain; and  
the polypeptide modulates the activity of a cell surface receptor.

212. The polypeptide of claim 211, wherein the CSR is an RTK.

20       213. A method of preparing a synthetic intron fusion protein, comprising:  
linking the N-terminus of one cell surface receptor isoform to an intron from a intron fusion protein.

214. The method of claim 213, wherein the linkage is covalent.

215. The method of claim 213, wherein the linkage is peptidic.

25       216. The method of claim 213, wherein the CSR isoform is an intron fusion protein.

217. A pharmaceutical composition, comprising a polypeptide, chimeric polypeptide or conjugate of any of claims 200-212.

218. A method of treating a disease or condition comprising, administering  
30       a pharmaceutical composition of claim 217.

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219. The method of claim 218, wherein the disease or condition is selected from the group consisting of cancers, inflammatory diseases, infectious diseases, angiogenesis-related conditions, cell proliferation-related conditions, immune disorders and neurodegenerative diseases.

5           220. The method of claim 218, wherein the disease or condition is selected from the group consisting of rheumatoid arthritis, multiple sclerosis, posterior intraocular inflammation, uveitic disorders, ocular surface inflammatory disorders, neovascular disease, proliferative vitreoretinopathy, atherosclerosis, rheumatoid arthritis, hemangioma, diabetes mellitus, inflammatory bowel disease, psoriasis,  
10 Alzheimer's disease, lupus, vascular stenosis, restenosis, inflammatory joint disease, atherosclerosis, urinary obstructive syndromes, and asthma.

221. The method of claim 218, wherein the disease or condition is selected from the group consisting of carcinoma, lymphoma, blastoma, sarcoma, leukemia, lymphoid malignancies, squamous cell cancer, small-cell lung cancer, non-small cell  
15 lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric cancer, stomach cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney/renal  
20 cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, and head and neck cancer.

222. The method of claim 218, wherein the disease or condition is infection by a virus or a parasite.

223. The method of claim 222, wherein the virus is selected from the group  
25 consisting of Myxoma virus, Vaccinia virus, Tanapox virus, Epstein-Barr virus, Herpes simplex virus, Cytomegalovirus, Herpesvirus saimiri, Hepatitis B virus, African swine fever virus, Parovirus, Human Immune deficiency virus (HIV), Hepatitis C virus, Influenza virus, Respiratory syncytial virus, Measles virus, Vesicular stomatitis virus, Dengue virus and Ebola virus.



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224. The method of claim 218, wherein the pharmaceutical composition contains a polypeptide that inhibits angiogenesis, cell proliferation, cell migration, viral entry, viral infection, tumor cell growth or tumor cell metastasis.

225. A method of regulating development and/or disease states, comprising  
5 contacting cells or tissues *in vitro* or *in vivo* with a polypeptide, chimeric polypeptide or conjugate of any of claims 1-143, 165-177, 200-212, thereby ameliorating the symptoms of the disease state or regulating development.

226. An isolated polypeptide, comprising at least one amino acid encoded by an intron of a gene encoding a polypeptide receptor isoform selected from among  
10 isoforms of FGFR-4, KIT, TNFRs, DDR1, FGFR-1, FGFR-4, VEGFR-2, VEGFR-3, RON, TEK, CSF1R, PDGFR-B, EphA, EphB, and MET.

227. The polypeptide of claim 226, wherein the polypeptide does not include a transmembrane domain.

228. The polypeptide of claim 226 or claim 227, that lacks at least one  
15 additional domain or a portion thereof whereby an activity is ablated or reduced or modified.

229. An isolated polypeptide of claim 226 that is a receptor antagonist.

230. A combination comprising:

two and one or more different cell surface receptor isoforms and/or a  
20 therapeutic drug or a cell surface receptor isoform and a therapeutic drug.

231. The combination of claim 230, wherein the isoforms and/or drugs are in separate compositions or in a single composition.

232. A method of treatment, comprising administering the components of the combination of claim 230, wherein each component is administered separately,  
25 simultaneously, intermittently, in a single composition or combinations thereof.

233. Use of a combination of claim 230 or claim 231 for the treatment of an angiogenic-related disorder, a tumor and/or an immune disorder.

234. Use of a combination of claim 230 or claim 231 for the formulation of a medicament for the treatment of angiogenic-related disorder, a tumor and/or an  
30 immune disorder.

# CSR Isoform targets in angiogenic and endothelial cell maintenance pathways

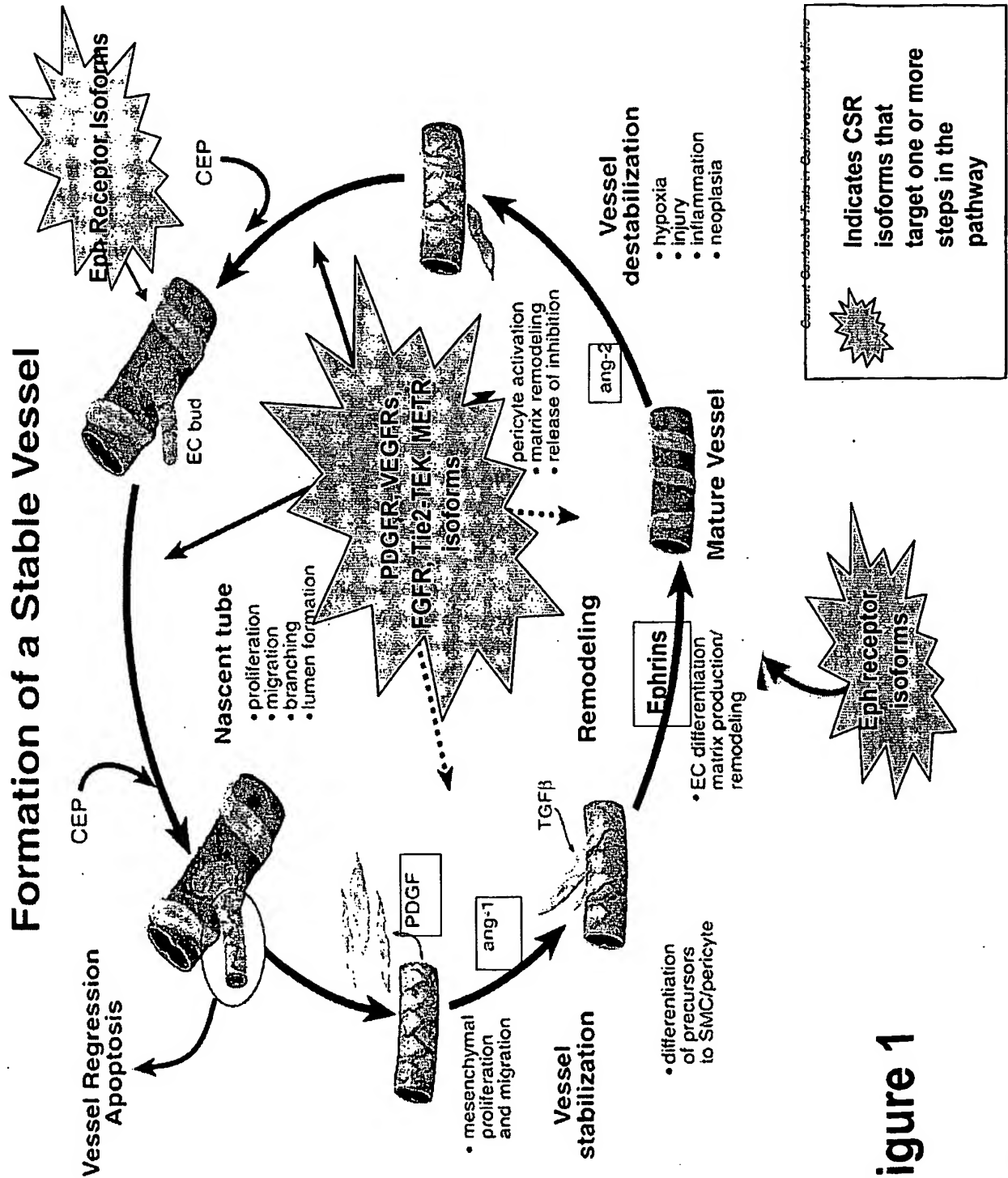


Figure 1

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<210> 78  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Primer VEGFR3\_R1

<400> 78  
aactcgggtcc aggtgtccag gc 22

<210> 79  
<211> 24  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Primer FLT3\_R2

<400> 79  
cttggaact cccatttgag atca 24

<210> 80  
<211> 21  
<212> DNA  
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<220>  
<223> Primer KIT\_R2

<400> 80  
acaaccttcc cgaaagctcc a 21

<210> 81  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Primer MET\_R2

<400> 81  
actacatgct gcactgcctg ga 22

- 21 -

<210> 82  
<211> 22  
<212> DNA  
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<220>  
<223> Primer PDGFRA\_R2

<400> 82  
cccgaccaag cactagtcca tc 22

<210> 83  
<211> 20  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Primer PDGFRB\_R2

<400> 83  
ccagagccga gggtagcgtcc 20

<210> 84  
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<220>  
<223> Primer RON\_R2

<400> 84  
caggtcattc aggttgggag ga 22

<210> 85  
<211> 24  
<212> DNA  
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<220>  
<223> Primer TEK\_R2

<400> 85  
atttgatgtc attccagtca agca 24

<210> 86  
<211> 21  
<212> DNA  
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<220>  
<223> Primer TIE\_R2

<400> 86  
agcactgggt agctcagggg c 21

<210> 87

- 22 -

<211> 21  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Primer VEGFR1\_R2

<400> 87  
 aactcccact tgctggcatc a 21

<210> 88  
 <211> 21  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Primer VEGFR2\_R2

<400> 88  
 aattcccatt tgctggcatc a 21

<210> 89  
 <211> 22  
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 <213> Artificial Sequence

<220>  
 <223> Primer VEGFR3\_R2

<400> 89  
 attcccactg gctggcatcg ta 22

<210> 90  
 <211> 713  
 <212> DNA  
 <213> Homo sapiens

<400> 90  
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 agcattcatc tatcactgtg tctgcgagag aggactggcc ttgcagggcg cagggcccta 180  
 agctgggctg cagagctggg gagccctgcc tggctcccag cctggagcag caagagcagg 240  
 agctgacagt agcccttggg cagcctgtgc gtctgtgctg tgggcgggct gagcgtggtg 300  
 gccactggta caaggagggc agtcgcctgg cacctgctgg ccgtgtacgg ggctggaggg 360  
 gccgcctaga gattgccagc ttcctacctg aggatgctgg ccgctacctc tgcctggcac 420  
 gaggtcccat gatcgtcctg cagaatctca ccttgattac aggtgactcc ttgacctcca 480  
 gcaacgatga tgaggacccc aagtccata gggaccctc gaataggcac agttaccccc 540  
 agcaagcacc ctactggaca cacccccagc gcatggagaa gaaactgcat gcagtacctg 600  
 cggggaacac cgtcaagttc cgctgtccag ctgcaggcaa cccacgccc accatccgct 660  
 ggcttaagga tggacaggcc tttcatgggg agaaccgcat tggaggcatt cgg 713

<210> 91  
 <211> 72  
 <212> PRT  
 <213> Homo sapiens



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&lt;400&gt; 91

```

Met Arg Leu Leu Leu Ala Leu Leu Gly Val Leu Leu Ser Val Pro Gly
 1           5           10           15
Pro Pro Val Leu Ser Leu Glu Ala Ser Glu Glu Val Glu Leu Ala Ser
          20           25           30
Ile His Leu Ser Leu Cys Leu Arg Glu Arg Thr Gly Leu Ala Gly Arg
          35           40           45
Arg Ala Leu Ser Trp Ala Ala Glu Leu Val Ser Pro Ala Trp Leu Pro
          50           55           60
Ala Trp Ser Ser Lys Ser Arg Ser
65                               70

```

&lt;210&gt; 92

&lt;211&gt; 1582

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 92

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gatcccatcg cagctaccgc gatgagagggc gctcgcgggcg cctgggattt tctctgcggt 60
ctgtctctac tgcttcgogt ccagacagggc tcttctcaac catctgtgag tccaggggaa 120
ccgtctccac catccatcca tccaggaaaa tcagacttaa tagtccgcgt gggcgacgag 180
attaggctgt tatgactga tccgggcttt gtcaaatgga cttttgagat cctggatgaa 240
acgaatgaga ataagcagaa tgaatggatc acggaaaagg cagaagccac caacaccggc 300
aaatacacgt gcaccaacaa acacggctta agcaattcca tttatgtgtt tgtagagat 360
cctgccaaagc ttttccttgt tgaccgctcc ttgtatggga aagaagacaa cgacacgctg 420
gtccgctgtc ctctcacaga cccagaagtg accaattatt ccctcaaggg gtgccagggg 480
aagcctcttc ccaaggactt gaggtttatt cctgacccca aggcgggcat catgatcaaa 540
agtgtgaaac gcgcctacca tcggctctgt ctgcattgtt ctgtggacca ggagggcaag 600
tcagtgtgtt cggaaaaatt catcctgaaa gtgaggccag ccttcaaagc tgtgcctgtt 660
gtgtctgtgt ccaaagcaag ctatcttctt agggaaagggg aagaattcac agtgacgtgc 720
acaataaaaag atgtgtctag ttctgtgtac tcaacgtgga aaagagaaaa cagtcagact 780
aaactacagg agaaatataa tagctggcat cacggtgact tcaattatga acgtcaggca 840
acgttgacta tcagttcagc gagagttaat gattctggag tgttcatgtg ttatgccaat 900
aatacttttg gatcagcaaa tgtcacaaac accttggaag tagtagataa aggattcatt 960
aatatcttcc ccattgataaa cactacagta tttgtaaacg atggagaaaa ttagattttg 1020
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accttctactg ataaatggga agattatccc aagtctgaga atgaaagtaa tatcagatac 1140
gtaagtgaac ttcatctaac gagattaaaa ggcaccgaag gaggcactta cacattccta 1200
gtgtccaatt ctgacgtcaa tgctgccata gcatttaatg tttatgtgaa tacttccctg 1260
taaatagagt gattcggctt ttaatcggca ccacccttcc acccccaaaa aggagaaaat 1320
tcatcaaaac cagaaatcct gacttacgac aggctcgtga atggcatgct ccaatgtgtg 1380
gcagcaggat tcccagagcc cacaatagat tggatTTTT gtccaggaaac tgagcagaga 1440
tgctctgctt ctgtactgcc agtggatgtg cagacactaa actcatctgg gccaccgttt 1500
ggaaagctag tggttcagag ttctatagat tctagtgcac tcaagcacia tggcacggtt 1560
gaatgtaagg cttacaacga tg
1582

```

&lt;210&gt; 93

&lt;211&gt; 413

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 93

```

Met Arg Gly Ala Arg Gly Ala Trp Asp Phe Leu Cys Val Leu Leu Leu
 1           5           10           15
Leu Leu Arg Val Gln Thr Gly Ser Ser Gln Pro Ser Val Ser Pro Gly

```

			20			25			30						
Glu	Pro	Ser	Pro	Pro	Ser	Ile	His	Pro	Gly	Lys	Ser	Asp	Leu	Ile	Val
35						40						45			
Arg	Val	Gly	Asp	Glu	Ile	Arg	Leu	Leu	Cys	Thr	Asp	Pro	Gly	Phe	Val
50						55						60			
Lys	Trp	Thr	Phe	Glu	Ile	Leu	Asp	Glu	Thr	Asn	Glu	Asn	Lys	Gln	Asn
65				70						75			80		
Glu	Trp	Ile	Thr	Glu	Lys	Ala	Glu	Ala	Thr	Asn	Thr	Gly	Lys	Tyr	Thr
			85						90			95			
Cys	Thr	Asn	Lys	His	Gly	Leu	Ser	Asn	Ser	Ile	Tyr	Val	Phe	Val	Arg
			100			105						110			
Asp	Pro	Ala	Lys	Leu	Phe	Leu	Val	Asp	Arg	Ser	Leu	Tyr	Gly	Lys	Glu
115						120						125			
Asp	Asn	Asp	Thr	Leu	Val	Arg	Cys	Pro	Leu	Thr	Asp	Pro	Glu	Val	Thr
130						135						140			
Asn	Tyr	Ser	Leu	Lys	Gly	Cys	Gln	Gly	Lys	Pro	Leu	Pro	Lys	Asp	Leu
145				150						155			160		
Arg	Phe	Ile	Pro	Asp	Pro	Lys	Ala	Gly	Ile	Met	Ile	Lys	Ser	Val	Lys
			165						170			175			
Arg	Ala	Tyr	His	Arg	Leu	Cys	Leu	His	Cys	Ser	Val	Asp	Gln	Glu	Gly
			180			185						190			
Lys	Ser	Val	Leu	Ser	Glu	Lys	Phe	Ile	Leu	Lys	Val	Arg	Pro	Ala	Phe
195						200						205			
Lys	Ala	Val	Pro	Val	Val	Ser	Val	Ser	Lys	Ala	Ser	Tyr	Leu	Leu	Arg
210						215						220			
Glu	Gly	Glu	Glu	Phe	Thr	Val	Thr	Cys	Thr	Ile	Lys	Asp	Val	Ser	Ser
225				230						235			240		
Ser	Val	Tyr	Ser	Thr	Trp	Lys	Arg	Glu	Asn	Ser	Gln	Thr	Lys	Leu	Gln
			245						250			255			
Glu	Lys	Tyr	Asn	Ser	Trp	His	His	Gly	Asp	Phe	Asn	Tyr	Glu	Arg	Gln
			260			265						270			
Ala	Thr	Leu	Thr	Ile	Ser	Ser	Ala	Arg	Val	Asn	Asp	Ser	Gly	Val	Phe
275						280						285			
Met	Cys	Tyr	Ala	Asn	Asn	Thr	Phe	Gly	Ser	Ala	Asn	Val	Thr	Thr	Thr
290						295						300			
Leu	Glu	Val	Val	Asp	Lys	Gly	Phe	Ile	Asn	Ile	Phe	Pro	Met	Ile	Asn
305				310						315			320		
Thr	Thr	Val	Phe	Val	Asn	Asp	Gly	Glu	Asn	Val	Asp	Leu	Ile	Val	Glu
			325						330			335			
Tyr	Glu	Ala	Phe	Pro	Lys	Pro	Glu	His	Gln	Gln	Trp	Ile	Tyr	Met	Asn
			340			345						350			
Arg	Thr	Phe	Thr	Asp	Lys	Trp	Glu	Asp	Tyr	Pro	Lys	Ser	Glu	Asn	Glu
355						360						365			
Ser	Asn	Ile	Arg	Tyr	Val	Ser	Glu	Leu	His	Leu	Thr	Arg	Leu	Lys	Gly
370						375						380			
Thr	Glu	Gly	Gly	Thr	Tyr	Thr	Phe	Leu	Val	Ser	Asn	Ser	Asp	Val	Asn
385				390						395			400		
Ala	Ala	Ile	Ala	Phe	Asn	Val	Tyr	Val	Asn	Thr	Ser	Leu			
			405						410						

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<210> 94
<211> 913
<212> DNA
<213> Homo sapiens
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&lt;400&gt; 94

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agaaggcgct gggctgcgag ggcgcgaggg cgcgagggca gggggcaacc ggaccccgcc 60
cgcacccatg gcgcccgtcg ccgtctgggc cgcgctggcc gtcggactgg agctctgggc 120
tgcggcgcac gccttgcccg cccaggtggc atttacacc tacgcccgg agcccgggag 180
cacatgccgg ctcagagaat actatgacca gacagctcag atgtgctgca gcaaatgctc 240
gccggggccaa catgcaaaag tcttctgtac caagacctcg gacaccgtgt gtgactcctg 300
tgaggacagc acatacacc agctctggaa ctgggttccc gagtgttga gctgtggctc 360
ccgctgtagc tctgaccagg tggaaactca agcctgcact cgggaacaga accgcatctg 420
cacctgcagg cccggctggt actgcgcgt gagcaagcag gaggggtgcc ggctgtgctc 480
gccgctgctc aagtgccgcc cgggcttcgg cgtggccaga ccagacctct cctagggtctc 540
tagtgccaag gccagctgt ccgcagagt gtctgagtgg ttgacaagtt cggattgttc 600
cctgaaggaa ctgaaacatc agacgtggtg tgcaagccct gtgccccggg gacgttcttc 660
aacacgactt catccacgga tatttgcagg cccaccaga tctgtaacgt ggtggccatc 720
cctgggaatg caagcatgga tgcagtctgc acgtccacgt ccccccaccg gagtatggcc 780
ccaggggcag tacacttacc ccagccagtg tccacacgat cccaacacac gcagccaact 840
ccagaaccga gcactgctcc aagcacctcc ttcctgctcc caatgggccc cagcccccca 900
gctgaaggga gca

```

&lt;210&gt; 95

&lt;211&gt; 155

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 95

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Met Ala Pro Val Ala Val Trp Ala Ala Leu Ala Val Gly Leu Glu Leu
1          5          10          15
Trp Ala Ala Ala His Ala Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr
20          25          30
Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Asp Gln
35          40          45
Thr Ala Gln Met Cys Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys
50          55          60
Val Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp
65          70          75          80
Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu Ser Cys
85          90          95
Gly Ser Arg Cys Ser Ser Asp Gln Val Glu Thr Gln Ala Cys Thr Arg
100         105         110
Glu Gln Asn Arg Ile Cys Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu
115         120         125
Ser Lys Gln Glu Gly Cys Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg
130         135         140
Pro Gly Phe Gly Val Ala Arg Pro Asp Leu Ser
145         150         155

```

&lt;210&gt; 96

&lt;211&gt; 680

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 96

```

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
1          5          10          15
Pro Leu Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp
20          25          30

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Met	Lys	Leu	Arg	Leu	Pro	Ala	Ser	Pro	Glu	Thr	His	Leu	Asp	Met	Leu
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Arg	His	Leu	Tyr	Gln	Gly	Cys	Gln	Val	Val	Gln	Gly	Asn	Leu	Glu	Leu
	50					55					60				
Thr	Tyr	Leu	Pro	Thr	Asn	Ala	Ser	Leu	Ser	Phe	Leu	Gln	Asp	Ile	Gln
65					70					75				80	
Glu	Val	Gln	Gly	Tyr	Val	Leu	Ile	Ala	His	Asn	Gln	Val	Arg	Gln	Val
				85					90					95	
Pro	Leu	Gln	Arg	Leu	Arg	Ile	Val	Arg	Gly	Thr	Gln	Leu	Phe	Glu	Asp
			100					105					110		
Asn	Tyr	Ala	Leu	Ala	Val	Leu	Asp	Asn	Gly	Asp	Pro	Leu	Asn	Asn	Thr
	115						120					125			
Thr	Pro	Val	Thr	Gly	Ala	Ser	Pro	Gly	Gly	Leu	Arg	Glu	Leu	Gln	Leu
	130					135						140			
Arg	Ser	Leu	Thr	Glu	Ile	Leu	Lys	Gly	Gly	Val	Leu	Ile	Gln	Arg	Asn
145					150					155				160	
Pro	Gln	Leu	Cys	Tyr	Gln	Asp	Thr	Ile	Leu	Trp	Lys	Asp	Ile	Phe	His
				165					170					175	
Lys	Asn	Asn	Gln	Leu	Ala	Leu	Thr	Leu	Ile	Asp	Thr	Asn	Arg	Ser	Arg
			180					185					190		
Ala	Cys	His	Pro	Cys	Ser	Pro	Met	Cys	Lys	Gly	Ser	Arg	Cys	Trp	Gly
	195						200					205			
Glu	Ser	Ser	Glu	Asp	Cys	Gln	Ser	Leu	Thr	Arg	Thr	Val	Cys	Ala	Gly
	210					215					220				
Gly	Cys	Ala	Arg	Cys	Lys	Gly	Pro	Leu	Pro	Thr	Asp	Cys	Cys	His	Glu
225					230						235			240	
Gln	Cys	Ala	Ala	Gly	Cys	Thr	Gly	Pro	Lys	His	Ser	Asp	Cys	Leu	Ala
				245					250					255	
Cys	Leu	His	Phe	Asn	His	Ser	Gly	Ile	Cys	Glu	Leu	His	Cys	Pro	Ala
			260					265					270		
Leu	Val	Thr	Tyr	Asn	Thr	Asp	Thr	Phe	Glu	Ser	Met	Pro	Asn	Pro	Glu
	275						280						285		
Gly	Arg	Tyr	Thr	Phe	Gly	Ala	Ser	Cys	Val	Thr	Ala	Cys	Pro	Tyr	Asn
	290					295					300				
Tyr	Leu	Ser	Thr	Asp	Val	Gly	Ser	Cys	Thr	Leu	Val	Cys	Pro	Leu	His
305					310					315				320	
Asn	Gln	Glu	Val	Thr	Ala	Glu	Asp	Gly	Thr	Gln	Arg	Cys	Glu	Lys	Cys
				325					330					335	
Ser	Lys	Pro	Cys	Ala	Arg	Val	Cys	Tyr	Gly	Leu	Gly	Met	Glu	His	Leu
			340					345					350		
Arg	Glu	Val	Arg	Ala	Val	Thr	Ser	Ala	Asn	Ile	Gln	Glu	Phe	Ala	Gly
			355				360					365			
Cys	Lys	Lys	Ile	Phe	Gly	Ser	Leu	Ala	Phe	Leu	Pro	Glu	Ser	Phe	Asp
	370					375					380				
Gly	Asp	Pro	Ala	Ser	Asn	Thr	Ala	Pro	Leu	Gln	Pro	Glu	Gln	Leu	Gln
385					390					395				400	
Val	Phe	Glu	Thr	Leu	Glu	Glu	Ile	Thr	Gly	Tyr	Leu	Tyr	Ile	Ser	Ala
				405					410					415	
Trp	Pro	Asp	Ser	Leu	Pro	Asp	Leu	Ser	Val	Phe	Gln	Asn	Leu	Gln	Val
			420					425					430		
Ile	Arg	Gly	Arg	Ile	Leu	His	Asn	Gly	Ala	Tyr	Ser	Leu	Thr	Leu	Gln
	435						440					445			
Gly	Leu	Gly	Ile	Ser	Trp	Leu	Gly	Leu	Arg	Ser	Leu	Arg	Glu	Leu	Gly
	450					455					460				
Ser	Gly	Leu	Ala	Leu	Ile	His	His	Asn	Thr	His	Leu	Cys	Phe	Val	His
465					470					475				480	

Thr	Val	Pro	Trp	Asp 485	Gln	Leu	Phe	Arg	Asn 490	Pro	His	Gln	Ala	Leu 495	Leu
His	Thr	Ala	Asn 500	Arg	Pro	Glu	Asp	Glu 505	Cys	Val	Gly	Glu	Gly 510	Leu	Ala
Cys	His	Gln 515	Leu	Cys	Ala	Arg	Gly 520	His	Cys	Trp	Gly	Pro 525	Gly	Pro	Thr
Gln	Cys	Val 530	Asn	Cys	Ser	Gln 535	Phe	Leu	Arg	Gly	Gln 540	Glu	Cys	Val	Glu
Glu 545	Cys	Arg	Val	Leu	Gln 550	Gly	Leu	Pro	Arg	Glu 555	Tyr	Val	Asn	Ala	Arg 560
His	Cys	Leu	Pro	Cys 565	His	Pro	Glu	Cys	Gln 570	Pro	Gln	Asn	Gly	Ser 575	Val
Thr	Cys	Phe 580	Gly	Pro	Glu	Ala	Asp 585	Gln	Cys	Val	Ala	Cys	Ala 590	His	Tyr
Lys	Asp 595	Pro	Pro	Phe	Cys	Val	Ala 600	Arg	Cys	Pro	Ser	Gly 605	Val	Lys	Pro
Asp	Leu 610	Ser	Tyr	Met	Pro	Ile 615	Trp	Lys	Phe	Pro	Asp 620	Glu	Glu	Gly	Ala
Cys 625	Gln	Pro	Cys	Pro 630	Ile	Asn	Cys	Thr	His 635	Ser	Cys	Val	Asp	Leu	Asp 640
Asp	Lys	Gly	Cys	Pro 645	Ala	Glu	Gln	Arg	Ala 650	Arg	Leu	Ala	Trp	Thr 655	Pro
Gly	Cys	Thr 660	Leu	His	Cys	Pro	Ser	Leu 665	Pro	His	Trp	Met	Leu 670	Gly	Gly
His	Cys 675	Cys	Arg	Glu	Gly	Thr	Pro 680								

<400> 97															
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1				5					10					15	
Pro	Pro	Gly	Ala	Ala	Ser	Thr	Gln	Val	Cys	Thr	Gly	Thr	Asp	Met	Lys
			20					25					30		
Leu	Arg	Leu	Pro	Ala	Ser	Pro	Glu	Thr	His	Leu	Asp	Met	Leu	Arg	His
	35						40					45			
Leu	Tyr	Gln	Gly	Cys	Gln	Val	Val	Gln	Gly	Asn	Leu	Glu	Leu	Thr	Tyr
	50					55					60				
Leu	Pro	Thr	Asn	Ala	Ser	Leu	Ser	Phe	Leu	Gln	Asp	Ile	Gln	Glu	Val
65					70					75					80
Gln	Gly	Tyr	Val	Leu	Ile	Ala	His	Asn	Gln	Val	Arg	Gln	Val	Pro	Leu
				85					90					95	
Gln	Arg	Leu	Arg	Ile	Val	Arg	Gly	Thr	Gln	Leu	Phe	Glu	Asp	Asn	Tyr
			100					105					110		
Ala	Leu	Ala	Val	Leu	Asp	Asn	Gly	Asp	Pro	Leu	Asn	Asn	Thr	Thr	Pro
		115					120					125			
Val	Thr	Gly	Ala	Ser	Pro	Gly	Gly	Leu	Arg	Glu	Leu	Gln	Leu	Arg	Ser
	130					135					140				
Leu	Thr	Glu	Ile	Leu	Lys	Gly	Gly	Val	Leu	Ile	Gln	Arg	Asn	Pro	Gln
145					150					155					160
Leu	Cys	Tyr	Gln	Asp	Thr	Ile	Leu	Trp	Lys	Asp	Ile	Phe	His	Lys	Asn
				165					170					175	

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Asn	Gln	Leu	Ala	Leu	Thr	Leu	Ile	Asp	Thr	Asn	Arg	Ser	Arg	Ala	Cys
			180					185					190		
His	Pro	Cys	Ser	Pro	Met	Cys	Lys	Gly	Ser	Arg	Cys	Trp	Gly	Glu	Ser
		195					200					205			
Ser	Glu	Asp	Cys	Gln	Ser	Leu	Thr	Arg	Thr	Val	Cys	Ala	Gly	Gly	Cys
	210					215					220				
Ala	Arg	Cys	Lys	Gly	Pro	Leu	Pro	Thr	Asp	Cys	Cys	His	Glu	Gln	Cys
225					230					235					240
Ala	Ala	Gly	Cys	Thr	Gly	Pro	Lys	His	Ser	Asp	Cys	Leu	Ala	Cys	Leu
				245					250					255	
His	Phe	Asn	His	Ser	Gly	Ile	Cys	Glu	Leu	His	Cys	Pro	Ala	Leu	Val
		260						265					270		
Thr	Tyr	Asn	Thr	Asp	Thr	Phe	Glu	Ser	Met	Pro	Asn	Pro	Glu	Gly	Arg
		275					280					285			
Tyr	Thr	Phe	Gly	Ala	Ser	Cys	Val	Thr	Ala	Cys	Pro	Tyr	Asn	Tyr	Leu
	290					295					300				
Ser	Thr	Asp	Val	Gly	Ser	Cys	Thr	Leu	Val	Cys	Pro	Leu	His	Asn	Gln
305					310					315					320
Glu	Val	Thr	Ala	Glu	Asp	Gly	Thr	Gln	Arg	Cys	Glu	Lys	Cys	Ser	Lys
				325					330					335	
Pro	Cys	Ala	Arg	Val	Cys	Tyr	Gly	Leu	Gly	Met	Glu	His	Leu	Arg	Glu
			340					345					350		
Val	Arg	Ala	Val	Thr	Ser	Ala	Asn	Ile	Gln	Glu	Phe	Ala	Gly	Cys	Lys
		355					360					365			
Lys	Ile	Phe	Gly	Ser	Leu	Ala	Phe	Leu	Pro	Glu	Ser	Phe	Asp	Gly	Asp
	370					375					380				
Pro	Ala	Ser	Asn	Thr	Ala	Pro	Leu	Gln	Pro	Glu	Gln	Leu	Gln	Val	Phe
385					390					395					400
Glu	Thr	Leu	Glu	Glu	Ile	Thr	Gly	Tyr	Leu	Tyr	Ile	Ser	Ala	Trp	Pro
				405					410					415	
Asp	Ser	Leu	Pro	Asp	Leu	Ser	Val	Phe	Gln	Asn	Leu	Gln	Val	Ile	Arg
		420						425					430		
Gly	Arg	Ile	Leu	His	Asn	Gly	Ala	Tyr	Ser	Leu	Thr	Leu	Gln	Gly	Leu
		435					440					445			
Gly	Ile	Ser	Trp	Leu	Gly	Leu	Arg	Ser	Leu	Arg	Glu	Leu	Gly	Ser	Gly
	450					455					460				
Leu	Ala	Leu	Ile	His	His	Asn	Thr	His	Leu	Cys	Phe	Val	His	Thr	Val
465					470					475					480
Pro	Trp	Asp	Gln	Leu	Phe	Arg	Asn	Pro	His	Gln	Ala	Leu	Leu	His	Thr
				485					490					495	
Ala	Asn	Arg	Pro	Glu	Asp	Glu	Cys	Val	Gly	Glu	Gly	Leu	Ala	Cys	His
			500					505					510		
Gln	Leu	Cys	Ala	Arg	Gly	His	Cys	Trp	Gly	Pro	Gly	Pro	Thr	Gln	Cys
		515						520					525		
Val	Asn	Cys	Ser	Gln	Phe	Leu	Arg	Gly	Gln	Glu	Cys	Val	Glu	Glu	Cys
	530					535					540				
Arg	Val	Leu	Gln	Gly	Leu	Pro	Arg	Glu	Tyr	Val	Asn	Ala	Arg	His	Cys
545					550					555					560
Leu	Pro	Cys	His	Pro	Glu	Cys	Gln	Pro	Gln	Asn	Gly	Ser	Val	Thr	Cys
				565					570					575	
Phe	Gly	Pro	Glu	Ala	Asp	Gln	Cys	Val	Ala	Cys	Ala	His	Tyr	Lys	Asp
			580					585					590		
Pro	Pro	Phe	Cys	Val	Ala	Arg	Cys	Pro	Ser	Gly	Val	Lys	Pro	Asp	Leu
		595					600					605			
Ser	Tyr	Met	Pro	Ile	Trp	Lys	Phe	Pro	Asp	Glu	Glu	Gly	Ala	Cys	Gln
	610					615					620				

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Pro Cys Pro Ile Asn Cys Thr His Ser  
625 630

<210> 98  
<211> 575  
<212> PRT  
<213> Homo sapiens

<400> 98  
Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu  
1 5 10 15  
Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys  
20 25 30  
Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His  
35 40 45  
Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr  
50 55 60  
Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val  
65 70 75 80  
Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu  
85 90 95  
Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr  
100 105 110  
Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro  
115 120 125  
Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser  
130 135 140  
Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln  
145 150 155 160  
Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn  
165 170 175  
Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys  
180 185 190  
His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser  
195 200 205  
Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys  
210 215 220  
Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys  
225 230 235 240  
Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu  
245 250 255  
His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val  
260 265 270  
Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg  
275 280 285  
Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu  
290 295 300  
Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln  
305 310 315 320  
Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys  
325 330 335  
Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu  
340 345 350  
Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys  
355 360 365

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Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp  
 370 375 380  
 Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe  
 385 390 395 400  
 Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro  
 405 410 415  
 Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg  
 420 425 430  
 Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu  
 435 440 445  
 Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly  
 450 455 460  
 Leu Ala Leu Ile His His Tyr Thr His Leu Cys Phe Val His Thr Val  
 465 470 475 480  
 Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr  
 485 490 495  
 Ala Asn Arg Pro Glu Asp Glu Cys Gly Lys Thr Gly Ser Pro Val Cys  
 500 505 510  
 Ala Leu Pro Ile Cys Gln His Thr Ala Val Pro Arg Gly Pro Trp Gln  
 515 520 525  
 Gln Arg Ser Trp Thr Cys Ala Asp Cys Pro Ser Leu Cys Thr Leu Leu  
 530 535 540  
 Asp Ser Ala Gln Leu Trp Leu Ala Trp Pro Leu Gly Met Ala Ser Leu  
 545 550 555 560  
 Ala Gly Ser Tyr Leu Pro Trp His Pro Ser Leu Pro Leu Cys Phe  
 565 570 575

&lt;210&gt; 99

&lt;211&gt; 523

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 99

Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser  
 1 5 10 15  
 Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Lys Leu Lys Asp Pro  
 20 25 30  
 Glu Leu Ser Leu Lys Gly Thr Gln His Ile Met Gln Ala Gly Gln Thr  
 35 40 45  
 Leu His Leu Gln Cys Arg Gly Glu Ala Ala His Lys Trp Ser Leu Pro  
 50 55 60  
 Glu Met Val Ser Lys Glu Ser Glu Arg Leu Ser Ile Thr Lys Ser Ala  
 65 70 75 80  
 Cys Gly Arg Asn Gly Lys Gln Phe Cys Ser Thr Leu Thr Leu Asn Thr  
 85 90 95  
 Ala Gln Ala Asn His Thr Gly Phe Tyr Ser Cys Lys Tyr Leu Ala Val  
 100 105 110  
 Pro Thr Ser Lys Lys Lys Glu Thr Glu Ser Ala Ile Tyr Ile Phe Ile  
 115 120 125  
 Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu  
 130 135 140  
 Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val  
 145 150 155 160  
 Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr  
 165 170 175



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Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe
      180      185      190
Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu
      195      200      205
Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg
      210      215      220
Gln Thr Asn Thr Ile Ile Asp Val Gln Ile Ser Thr Pro Arg Pro Val
225      230      235      240
Lys Leu Leu Arg Gly His Thr Leu Val Leu Asn Cys Thr Ala Thr Thr
      245      250      255
Pro Leu Asn Thr Arg Val Gln Met Thr Trp Ser Tyr Pro Asp Glu Lys
      260      265      270
Asn Lys Arg Ala Ser Val Arg Arg Ile Asp Gln Ser Asn Ser His
      275      280      285
Ala Asn Ile Phe Tyr Ser Val Leu Thr Ile Asp Lys Met Gln Asn Lys
      290      295      300
Asp Lys Gly Leu Tyr Thr Cys Arg Val Arg Ser Gly Pro Ser Phe Lys
305      310      315      320
Ser Val Asn Thr Ser Val His Ile Tyr Asp Lys Ala Phe Ile Thr Val
      325      330      335
Lys His Arg Lys Gln Gln Val Leu Glu Thr Val Ala Gly Lys Arg Ser
      340      345      350
Tyr Arg Leu Ser Met Lys Val Lys Ala Phe Pro Ser Pro Glu Val Val
      355      360      365
Trp Leu Lys Asp Gly Leu Pro Ala Thr Glu Lys Ser Ala Arg Tyr Leu
      370      375      380
Thr Arg Gly Tyr Ser Leu Ile Ile Lys Asp Val Thr Glu Glu Asp Ala
385      390      395      400
Gly Asn Tyr Thr Ile Leu Leu Ser Ile Lys Gln Ser Asn Val Phe Lys
      405      410      415
Asn Leu Thr Ala Thr Leu Ile Val Asn Val Lys Pro Gln Ile Tyr Glu
      420      425      430
Ile Leu Thr Cys Thr Ala Tyr Gly Ile Pro Gln Pro Thr Ile Lys Trp
      435      440      445
Phe Trp His Pro Cys Asn His Asn His Ser Glu Ala Arg Cys Asp Phe
      450      455      460
Cys Ser Asn Asn Glu Glu Ser Phe Ile Leu Asp Ala Asp Ser Asn Met
465      470      475      480
Gly Asn Arg Ile Glu Ser Ile Thr Gln Arg Met Ala Ile Ile Glu Gly
      485      490      495
Lys Asn Lys Leu Pro Pro Ala Asn Ser Ser Phe Met Leu Pro Pro Thr
      500      505      510
Ser Phe Ser Ser Asn Tyr Phe His Phe Leu Pro
      515      520

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&lt;210&gt; 100

&lt;211&gt; 541

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 100

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Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
 1      5      10      15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Lys Leu Lys Asp Pro
      20      25      30

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Glu	Leu	Ser	Leu	Lys	Gly	Thr	Gln	His	Ile	Met	Gln	Ala	Gly	Gln	Thr
	35						40				45				
Leu	His	Leu	Gln	Cys	Arg	Gly	Glu	Ala	Ala	His	Lys	Trp	Ser	Leu	Pro
50						55					60				
Glu	Met	Val	Ser	Lys	Glu	Ser	Glu	Arg	Leu	Ser	Ile	Thr	Lys	Ser	Ala
65					70					75					80
Cys	Gly	Arg	Asn	Gly	Lys	Gln	Phe	Cys	Ser	Thr	Leu	Thr	Leu	Asn	Thr
				85					90					95	
Ala	Gln	Ala	Asn	His	Thr	Gly	Phe	Tyr	Ser	Cys	Lys	Tyr	Leu	Ala	Val
			100					105					110		
Pro	Thr	Ser	Lys	Lys	Lys	Glu	Thr	Glu	Ser	Ala	Ile	Tyr	Ile	Phe	Ile
	115						120					125			
Ser	Asp	Thr	Gly	Arg	Pro	Phe	Val	Glu	Met	Tyr	Ser	Glu	Ile	Pro	Glu
	130					135					140				
Ile	Ile	His	Met	Thr	Glu	Gly	Arg	Glu	Leu	Val	Ile	Pro	Cys	Arg	Val
145					150					155					160
Thr	Ser	Pro	Asn	Ile	Thr	Val	Thr	Leu	Lys	Lys	Phe	Pro	Leu	Asp	Thr
			165					170						175	
Leu	Ile	Pro	Asp	Gly	Lys	Arg	Ile	Ile	Trp	Asp	Ser	Arg	Lys	Gly	Phe
			180					185					190		
Ile	Ile	Ser	Asn	Ala	Thr	Tyr	Lys	Glu	Ile	Gly	Leu	Leu	Thr	Cys	Glu
	195						200					205			
Ala	Thr	Val	Asn	Gly	His	Leu	Tyr	Lys	Thr	Asn	Tyr	Leu	Thr	His	Arg
	210					215					220				
Gln	Thr	Asn	Thr	Ile	Ile	Asp	Val	Gln	Ile	Ser	Thr	Pro	Arg	Pro	Val
225					230					235					240
Lys	Leu	Leu	Arg	Gly	His	Thr	Leu	Val	Leu	Asn	Cys	Thr	Ala	Thr	Thr
			245						250					255	
Pro	Leu	Asn	Thr	Arg	Val	Gln	Met	Thr	Trp	Ser	Tyr	Pro	Asp	Glu	Lys
		260						265					270		
Asn	Lys	Arg	Ala	Ser	Val	Arg	Arg	Ile	Asp	Gln	Ser	Asn	Ser	His	
	275						280				285				
Ala	Asn	Ile	Phe	Tyr	Ser	Val	Leu	Thr	Ile	Asp	Lys	Met	Gln	Asn	Lys
	290					295					300				
Asp	Lys	Gly	Leu	Tyr	Thr	Cys	Arg	Val	Arg	Ser	Gly	Pro	Ser	Phe	Lys
305					310					315					320
Ser	Val	Asn	Thr	Ser	Val	His	Ile	Tyr	Asp	Lys	Ala	Phe	Ile	Thr	Val
			325						330					335	
Lys	His	Arg	Lys	Gln	Gln	Val	Leu	Glu	Thr	Val	Ala	Gly	Lys	Arg	Ser
			340					345					350		
Tyr	Arg	Leu	Ser	Met	Lys	Val	Lys	Ala	Phe	Pro	Ser	Pro	Glu	Val	Val
	355						360					365			
Trp	Leu	Lys	Asp	Gly	Leu	Pro	Ala	Thr	Glu	Lys	Ser	Ala	Arg	Tyr	Leu
	370					375					380				
Thr	Arg	Gly	Tyr	Ser	Leu	Ile	Ile	Lys	Asp	Val	Thr	Glu	Glu	Asp	Ala
385					390				395						400
Gly	Asn	Tyr	Thr	Ile	Leu	Leu	Ser	Ile	Lys	Gln	Ser	Asn	Val	Phe	Lys
			405						410					415	
Asn	Leu	Thr	Ala	Thr	Leu	Ile	Val	Asn	Val	Lys	Pro	Gln	Ile	Tyr	Glu
		420						425					430		
Lys	Ala	Val	Ser	Ser	Phe	Pro	Asp	Pro	Ala	Leu	Tyr	Pro	Leu	Gly	Ser
	435						440					445			
Arg	Gln	Ile	Leu	Thr	Cys	Thr	Ala	Tyr	Gly	Ile	Pro	Gln	Pro	Thr	Ile
	450					455					460				
Lys	Trp	Phe	Trp	His	Pro	Cys	Asn	His	Asn	His	Ser	Glu	Ala	Arg	Cys
465					470					475					480

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Asp Phe Cys Ser Asn Asn Glu Glu Ser Phe Ile Leu Asp Ala Asp Ser
      485      490      495
Asn Met Gly Asn Arg Ile Glu Ser Ile Thr Gln Arg Met Ala Ile Ile
      500      505      510
Glu Gly Lys Asn Lys Leu Pro Pro Ala Asn Ser Ser Phe Met Leu Pro
      515      520      525
Pro Thr Ser Phe Ser Ser Asn Tyr Phe His Phe Leu Pro
      530      535      540

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<210> 101
<211> 436
<212> PRT
<213> Homo sapiens

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<400> 101
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
  1      5      10      15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Lys Leu Lys Asp Pro
      20      25      30
Glu Leu Ser Leu Lys Gly Thr Gln His Ile Met Gln Ala Gly Gln Thr
      35      40      45
Leu His Leu Gln Cys Arg Gly Glu Ala Ala His Lys Trp Ser Leu Pro
      50      55      60
Glu Met Val Ser Lys Glu Ser Glu Arg Leu Ser Ile Thr Lys Ser Ala
      65      70      75      80
Cys Gly Arg Asn Gly Lys Gln Phe Cys Ser Thr Leu Thr Leu Asn Thr
      85      90      95
Ala Gln Ala Asn His Thr Gly Phe Tyr Ser Cys Lys Tyr Leu Ala Val
      100      105      110
Pro Thr Ser Lys Lys Lys Glu Thr Glu Ser Ala Ile Tyr Ile Phe Ile
      115      120      125
Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu
      130      135      140
Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val
      145      150      155      160
Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr
      165      170      175
Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe
      180      185      190
Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu
      195      200      205
Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg
      210      215      220
Gln Thr Asn Thr Ile Ile Asp Val Gln Ile Ser Thr Pro Arg Pro Val
      225      230      235      240
Lys Leu Leu Arg Gly His Thr Leu Val Leu Asn Cys Thr Ala Thr Thr
      245      250      255
Pro Leu Asn Thr Arg Val Gln Met Thr Trp Ser Tyr Pro Asp Glu Lys
      260      265      270
Asn Lys Arg Ala Ser Val Arg Arg Arg Ile Asp Gln Ser Asn Ser His
      275      280      285
Ala Asn Ile Phe Tyr Ser Val Leu Thr Ile Asp Lys Met Gln Asn Lys
      290      295      300
Asp Lys Gly Leu Tyr Thr Cys Arg Val Arg Ser Gly Pro Ser Phe Lys
      305      310      315      320

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Ser Val Asn Thr Ser Val His Ile Tyr Asp Lys Ala Phe Ile Thr Val
      325      330      335
Lys His Arg Lys Gln Gln Val Leu Glu Thr Val Ala Gly Lys Arg Ser
      340      345      350
Tyr Arg Leu Ser Met Lys Val Lys Ala Phe Pro Ser Pro Glu Val Val
      355      360      365
Trp Leu Lys Asp Gly Leu Pro Ala Thr Glu Lys Ser Ala Arg Tyr Leu
      370      375      380
Thr Arg Gly Tyr Ser Leu Ile Ile Lys Asp Lys Asn Leu Thr Ala Thr
      385      390      395      400
Leu Ile Val Asn Val Lys Pro Gln Glu Arg Ile Arg Glu Arg Ile Ser
      405      410      415
Pro Asp Leu Tyr Arg Ile Trp Tyr Pro Ser Thr Tyr Asn Gln Val Val
      420      425      430
Leu Ala Pro Leu
      435

```

```

<210> 102
<211> 365
<212> PRT
<213> Homo sapiens

```

```

<400> 102
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
 1      5      10      15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Lys Leu Lys Asp Pro
      20      25      30
Glu Leu Ser Leu Lys Gly Thr Gln His Ile Met Gln Ala Gly Gln Thr
      35      40      45
Leu His Leu Gln Cys Arg Gly Glu Ala Ala His Lys Trp Ser Leu Pro
      50      55      60
Glu Met Val Ser Lys Glu Ser Glu Arg Leu Ser Ile Thr Lys Ser Ala
      65      70      75      80
Cys Gly Arg Asn Gly Lys Gln Phe Cys Ser Thr Leu Thr Leu Asn Thr
      85      90      95
Ala Gln Ala Asn His Thr Gly Phe Tyr Ser Cys Lys Tyr Leu Ala Val
      100      105      110
Pro Thr Ser Lys Lys Lys Glu Thr Glu Ser Ala Ile Tyr Ile Phe Ile
      115      120      125
Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu
      130      135      140
Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val
      145      150      155      160
Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr
      165      170      175
Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe
      180      185      190
Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu
      195      200      205
Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg
      210      215      220
Gln Thr Asn Thr Ile Ile Asp Val Gln Ile Ser Thr Pro Arg Pro Val
      225      230      235      240
Lys Leu Leu Arg Gly His Thr Leu Val Leu Asn Cys Thr Ala Thr Thr
      245      250      255

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Pro Leu Asn Thr Arg Val Gln Met Thr Trp Ser Tyr Pro Asp Glu Lys
      260      265      270
Asn Lys Arg Ala Ser Val Arg Arg Ile Asp Gln Ser Asn Ser His
      275      280      285
Ala Asn Ile Phe Tyr Ser Val Leu Thr Ile Asp Lys Met Gln Asn Lys
      290      295      300
Asp Lys Gly Leu Tyr Thr Cys Arg Val Arg Ser Gly Pro Ser Phe Lys
      305      310      315      320
Ser Val Asn Thr Ser Val His Ile Tyr Gly Lys His Ser Ser Ala Leu
      325      330      335
Pro Thr His Ala Met Leu Ser Asn His Cys Arg Cys Leu Cys Ser Leu
      340      345      350
Asn Lys Ser Val Phe Cys Trp Pro Arg Val Thr Leu Ser
      355      360      365

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```

<210> 103
<211> 934
<212> PRT
<213> Homo sapiens

```

```

<400> 103
Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
  1      5      10      15
Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys
      20      25      30
Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
      35      40      45
Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
      50      55      60
Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
      65      70      75      80
Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
      85      90      95
Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
      100      105      110
Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
      115      120      125
Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
      130      135      140
Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys
      145      150      155      160
Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val
      165      170      175
Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe
      180      185      190
Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp
      195      200      205
His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp
      210      215      220
Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu
      225      230      235      240
Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn
      245      250      255
Asn Phe Ile Tyr Phe Leu Thr Val Gln Arg Glu Thr Leu Asp Ala Gln
      260      265      270

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Thr	Phe	His	Thr	Arg	Ile	Ile	Arg	Phe	Cys	Ser	Ile	Asn	Ser	Gly	Leu
		275					280					285			
His	Ser	Tyr	Met	Glu	Met	Pro	Leu	Glu	Cys	Ile	Leu	Thr	Glu	Lys	Arg
		290					295				300				
Lys	Lys	Arg	Ser	Thr	Lys	Lys	Glu	Val	Phe	Asn	Ile	Leu	Gln	Ala	Ala
305					310					315					320
Tyr	Val	Ser	Lys	Pro	Gly	Ala	Gln	Leu	Ala	Arg	Gln	Ile	Gly	Ala	Ser
				325					330					335	
Leu	Asn	Asp	Asp	Ile	Leu	Phe	Gly	Val	Phe	Ala	Gln	Ser	Lys	Pro	Asp
			340					345					350		
Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser	Ala	Met	Cys	Ala	Phe	Pro	Ile	Lys
		355					360					365			
Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys	Ile	Val	Asn	Lys	Asn	Asn	Val	Arg
		370				375					380				
Cys	Leu	Gln	His	Phe	Tyr	Gly	Pro	Asn	His	Glu	His	Cys	Phe	Asn	Arg
385					390					395					400
Thr	Leu	Leu	Arg	Asn	Ser	Ser	Gly	Cys	Glu	Ala	Arg	Arg	Asp	Glu	Tyr
				405					410					415	
Arg	Thr	Glu	Phe	Thr	Thr	Ala	Leu	Gln	Arg	Val	Asp	Leu	Phe	Met	Gly
			420					425					430		
Gln	Phe	Ser	Glu	Val	Leu	Leu	Thr	Ser	Ile	Ser	Thr	Phe	Ile	Lys	Gly
		435					440					445			
Asp	Leu	Thr	Ile	Ala	Asn	Leu	Gly	Thr	Ser	Glu	Gly	Arg	Phe	Met	Gln
		450				455					460				
Val	Val	Val	Ser	Arg	Ser	Gly	Pro	Ser	Thr	Pro	His	Val	Asn	Phe	Leu
465					470					475					480
Leu	Asp	Ser	His	Pro	Val	Ser	Pro	Glu	Val	Ile	Val	Glu	His	Thr	Leu
				485					490					495	
Asn	Gln	Asn	Gly	Tyr	Thr	Leu	Val	Ile	Thr	Gly	Lys	Lys	Ile	Thr	Lys
		500						505					510		
Ile	Pro	Leu	Asn	Gly	Leu	Gly	Cys	Arg	His	Phe	Gln	Ser	Cys	Ser	Gln
		515					520					525			
Cys	Leu	Ser	Ala	Pro	Pro	Phe	Val	Gln	Cys	Gly	Trp	Cys	His	Asp	Lys
		530				535					540				
Cys	Val	Arg	Ser	Glu	Glu	Cys	Leu	Ser	Gly	Thr	Trp	Thr	Gln	Gln	Ile
545					550					555					560
Cys	Leu	Pro	Ala	Ile	Tyr	Lys	Val	Phe	Pro	Asn	Ser	Ala	Pro	Leu	Glu
				565					570					575	
Gly	Gly	Thr	Arg	Leu	Thr	Ile	Cys	Gly	Trp	Asp	Phe	Gly	Phe	Arg	Arg
			580					585					590		
Asn	Asn	Lys	Phe	Asp	Leu	Lys	Lys	Thr	Arg	Val	Leu	Leu	Gly	Asn	Glu
		595					600					605			
Ser	Cys	Thr	Leu	Thr	Leu	Ser	Glu	Ser	Thr	Met	Asn	Thr	Leu	Lys	Cys
		610				615					620				
Thr	Val	Gly	Pro	Ala	Met	Asn	Lys	His	Phe	Asn	Met	Ser	Ile	Ile	Ile
625					630					635					640
Ser	Asn	Gly	His	Gly	Thr	Thr	Gln	Tyr	Ser	Thr	Phe	Ser	Tyr	Val	Asp
				645					650					655	
Pro	Val	Ile	Thr	Ser	Ile	Ser	Pro	Lys	Tyr	Gly	Pro	Met	Ala	Gly	Gly
			660					665					670		
Thr	Leu	Leu	Thr	Leu	Thr	Gly	Asn	Tyr	Leu	Asn	Ser	Gly	Asn	Ser	Arg
		675					680					685			
His	Ile	Ser	Ile	Gly	Gly	Lys	Thr	Cys	Thr	Leu	Lys	Ser	Val	Ser	Asn
	690					695					700				
Ser	Ile	Leu	Glu	Cys	Tyr	Thr	Pro	Ala	Gln	Thr	Ile	Ser	Thr	Glu	Phe
705					710					715					720

[illegible]

```
<210> 104
<211> 821
<212> PRT
<213> Homo sapiens
```

<400> 104															
Met	Asp	Ser	Leu	Ala	Ser	Leu	Val	Leu	Cys	Gly	Val	Ser	Leu	Leu	Leu
1				5					10					15	
Ser	Gly	Thr	Val	Glu	Gly	Ala	Met	Asp	Leu	Ile	Leu	Ile	Asn	Ser	Leu
			20					25					30		
Pro	Leu	Val	Ser	Asp	Ala	Glu	Thr	Ser	Leu	Thr	Cys	Ile	Ala	Ser	Gly
		35					40					45			
Trp	Arg	Pro	His	Glu	Pro	Ile	Thr	Ile	Gly	Arg	Asp	Phe	Glu	Ala	Leu
50						55					60				
Met	Asn	Gln	His	Gln	Asp	Pro	Leu	Glu	Val	Thr	Gln	Asp	Val	Thr	Arg
65					70					75					80
Glu	Trp	Ala	Lys	Lys	Val	Val	Trp	Lys	Arg	Glu	Lys	Ala	Ser	Lys	Ile
				85					90					95	
Asn	Gly	Ala	Tyr	Phe	Cys	Glu	Gly	Arg	Val	Arg	Gly	Glu	Ala	Ile	Arg
			100					105					110		
Ile	Arg	Thr	Met	Lys	Met	Arg	Gln	Gln	Ala	Ser	Phe	Leu	Pro	Ala	Thr
		115					120					125			
Leu	Thr	Met	Thr	Val	Asp	Lys	Gly	Asp	Asn	Val	Asn	Ile	Ser	Phe	Lys
		130				135					140				
Lys	Val	Leu	Ile	Lys	Glu	Glu	Asp	Ala	Val	Ile	Tyr	Lys	Asn	Gly	Ser
145					150					155					160

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Phe	Ile	His	Ser	Val	Pro	Arg	His	Glu	Val	Pro	Asp	Ile	Leu	Glu	Val
				165					170					175	
His	Leu	Pro	His	Ala	Gln	Pro	Gln	Asp	Ala	Gly	Val	Tyr	Ser	Ala	Arg
				180					185					190	
Tyr	Ile	Gly	Gly	Asn	Leu	Phe	Thr	Ser	Ala	Phe	Thr	Arg	Leu	Ile	Val
		195					200					205			
Arg	Arg	Cys	Glu	Ala	Gln	Lys	Trp	Gly	Pro	Glu	Cys	Asn	His	Leu	Cys
		210				215					220				
Thr	Ala	Cys	Met	Asn	Asn	Gly	Val	Cys	His	Glu	Asp	Thr	Gly	Glu	Cys
225					230					235					240
Ile	Cys	Pro	Pro	Gly	Phe	Met	Gly	Arg	Thr	Cys	Glu	Lys	Ala	Cys	Glu
				245					250					255	
Leu	His	Thr	Phe	Gly	Arg	Thr	Cys	Lys	Glu	Arg	Cys	Ser	Gly	Gln	Glu
			260					265						270	
Gly	Cys	Lys	Ser	Tyr	Val	Phe	Cys	Leu	Pro	Asp	Pro	Tyr	Gly	Cys	Ser
		275					280					285			
Cys	Ala	Thr	Gly	Trp	Lys	Gly	Leu	Gln	Cys	Asn	Glu	Gly	Ile	Gln	Arg
		290				295					300				
Met	Thr	Pro	Lys	Ile	Val	Asp	Leu	Pro	Asp	His	Ile	Glu	Val	Asn	Ser
305					310					315					320
Gly	Lys	Phe	Asn	Pro	Ile	Cys	Lys	Ala	Ser	Gly	Trp	Pro	Leu	Pro	Thr
			325						330					335	
Asn	Glu	Glu	Met	Thr	Leu	Val	Lys	Pro	Asp	Gly	Thr	Val	Leu	His	Pro
			340					345					350		
Lys	Asp	Phe	Asn	His	Thr	Asp	His	Phe	Ser	Val	Ala	Ile	Phe	Thr	Ile
		355					360						365		
His	Arg	Ile	Leu	Pro	Pro	Asp	Ser	Gly	Val	Trp	Val	Cys	Ser	Val	Asn
		370				375					380				
Thr	Val	Ala	Gly	Met	Val	Glu	Lys	Pro	Phe	Asn	Ile	Ser	Val	Lys	Val
385					390					395					400
Leu	Pro	Lys	Pro	Leu	Asn	Ala	Pro	Asn	Val	Ile	Asp	Thr	Gly	His	Asn
				405					410					415	
Phe	Ala	Val	Ile	Asn	Ile	Ser	Ser	Glu	Pro	Tyr	Phe	Gly	Asp	Gly	Pro
			420					425					430		
Ile	Lys	Ser	Lys	Lys	Leu	Leu	Tyr	Lys	Pro	Val	Asn	His	Tyr	Glu	Ala
		435					440					445			
Trp	Gln	His	Ile	Gln	Val	Thr	Asn	Glu	Ile	Val	Thr	Leu	Asn	Tyr	Leu
		450				455					460				
Glu	Pro	Arg	Thr	Glu	Tyr	Glu	Leu	Cys	Val	Gln	Leu	Val	Arg	Arg	Gly
465					470					475					480
Glu	Gly	Gly	Glu	Gly	His	Pro	Gly	Pro	Val	Arg	Arg	Phe	Thr	Thr	Ala
				485					490					495	
Ser	Ile	Gly	Leu	Pro	Pro	Pro	Arg	Gly	Leu	Asn	Leu	Leu	Pro	Lys	Ser
			500					505					510		
Gln	Thr	Thr	Leu	Asn	Leu	Thr	Trp	Gln	Pro	Ser	Ser	Glu	Asp	Asp	Phe
		515					520					525			
Tyr	Val	Glu	Val	Glu	Arg	Arg	Ser	Val	Gln	Lys	Ser	Asp	Gln	Gln	Asn
		530				535					540				
Ile	Lys	Val	Pro	Gly	Asn	Leu	Thr	Ser	Val	Leu	Leu	Asn	Asn	Leu	His
545					550					555					560
Pro	Arg	Glu	Gln	Tyr	Val	Val	Arg	Ala	Arg	Val	Asn	Thr	Lys	Ala	Gln
				565					570					575	
Gly	Glu	Trp	Ser	Glu	Asp	Leu	Thr	Ala	Trp	Thr	Leu	Ser	Asp	Ile	Leu
			580				585						590		
Pro	Pro	Gln	Pro	Glu	Asn	Ile	Lys	Ile	Ser	Asn	Ile	Thr	His	Ser	Ser
			595				600					605			



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```

Ala Val Ile Ser Trp Thr Ile Leu Asp Gly Tyr Ser Ile Ser Ser Ile
  610                615                620
Thr Ile Arg Tyr Lys Val Gln Gly Lys Asn Glu Asp Gln His Val Asp
625                630                635                640
Val Lys Ile Lys Asn Ala Thr Ile Thr Gln Tyr Gln Leu Lys Gly Leu
                645                650                655
Glu Pro Glu Thr Ala Tyr Gln Val Asp Ile Phe Ala Glu Asn Asn Ile
                660                665                670
Gly Ser Ser Asn Pro Ala Phe Ser His Glu Leu Val Thr Leu Pro Glu
                675                680                685
Ser Gln Ala Pro Ala Asp Leu Gly Gly Gly Lys Met Leu Leu Ile Ala
        690                695                700
Ile Leu Gly Ser Ala Gly Met Thr Cys Leu Thr Val Leu Leu Ala Phe
705                710                715                720
Leu Ile Ile Leu Gln Leu Lys Arg Ala Asn Val Gln Arg Arg Met Ala
                725                730                735
Gln Ala Phe Gln Asn Val Arg Glu Glu Pro Ala Val Gln Phe Asn Ser
                740                745                750
Gly Thr Leu Ala Leu Asn Arg Lys Val Lys Asn Asn Pro Asp Pro Thr
                755                760                765
Ile Tyr Pro Val Leu Asp Trp Asn Asp Ile Lys Phe Gln Asp Val Ile
        770                775                780
Gly Glu Gly Asn Phe Gly Gln Val Leu Lys Ala Arg Ile Lys Lys Asp
785                790                795                800
Gly Leu Arg Met Asp Ala Ala Ile Lys Arg Met Lys Glu Tyr Ala Ser
                805                810                815
Lys Asp Asp His Arg
                820

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&lt;210&gt; 105

&lt;211&gt; 864

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 105

```

Met Asp Ser Leu Ala Ser Leu Val Leu Cys Gly Val Ser Leu Leu Leu
  1                5                10                15
Ser Gly Thr Val Glu Gly Ala Met Asp Leu Ile Leu Ile Asn Ser Leu
                20                25                30
Pro Leu Val Ser Asp Ala Glu Thr Ser Leu Thr Cys Ile Ala Ser Gly
        35                40                45
Trp Arg Pro His Glu Pro Ile Thr Ile Gly Arg Asp Phe Glu Ala Leu
        50                55                60
Met Asn Gln His Gln Asp Pro Leu Glu Val Thr Gln Asp Val Thr Arg
65                70                75                80
Glu Trp Ala Lys Lys Val Val Trp Lys Arg Glu Lys Ala Ser Lys Ile
                85                90                95
Asn Gly Ala Tyr Phe Cys Glu Gly Arg Val Arg Gly Glu Ala Ile Arg
                100                105                110
Ile Arg Thr Met Lys Met Arg Gln Gln Ala Ser Phe Leu Pro Ala Thr
        115                120                125
Leu Thr Met Thr Val Asp Lys Gly Asp Asn Val Asn Ile Ser Phe Lys
        130                135                140
Lys Val Leu Ile Lys Glu Glu Asp Ala Val Ile Tyr Lys Asn Gly Ser
145                150                155                160

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Phe	Ile	His	Ser	Val	Pro	Arg	His	Glu	Val	Pro	Asp	Ile	Leu	Glu	Val
				165					170					175	
His	Leu	Pro	His	Ala	Gln	Pro	Gln	Asp	Ala	Gly	Val	Tyr	Ser	Ala	Arg
			180					185					190		
Tyr	Ile	Gly	Gly	Asn	Leu	Phe	Thr	Ser	Ala	Phe	Thr	Arg	Leu	Ile	Val
	195						200					205			
Arg	Arg	Cys	Glu	Ala	Gln	Lys	Trp	Gly	Pro	Glu	Cys	Asn	His	Leu	Cys
	210					215					220				
Thr	Ala	Cys	Met	Asn	Asn	Gly	Val	Cys	His	Glu	Asp	Thr	Gly	Glu	Cys
225					230					235				240	
Ile	Cys	Pro	Pro	Gly	Phe	Met	Gly	Arg	Thr	Cys	Glu	Lys	Ala	Cys	Glu
				245					250					255	
Leu	His	Thr	Phe	Gly	Arg	Thr	Cys	Lys	Glu	Arg	Cys	Ser	Gly	Gln	Glu
			260					265					270		
Gly	Cys	Lys	Ser	Tyr	Val	Phe	Cys	Leu	Pro	Asp	Pro	Tyr	Gly	Cys	Ser
		275					280					285			
Cys	Ala	Thr	Gly	Trp	Lys	Gly	Leu	Gln	Cys	Asn	Glu	Ala	Cys	His	Pro
	290						295				300				
Gly	Phe	Tyr	Gly	Pro	Asp	Cys	Lys	Leu	Arg	Cys	Ser	Cys	Asn	Asn	Gly
305					310					315					320
Glu	Met	Cys	Asp	Arg	Phe	Gln	Gly	Cys	Leu	Cys	Ser	Pro	Gly	Trp	Gln
			325						330					335	
Gly	Leu	Gln	Cys	Glu	Arg	Glu	Gly	Ile	Gln	Arg	Met	Thr	Pro	Lys	Ile
			340					345					350		
Val	Asp	Leu	Pro	Asp	His	Ile	Glu	Val	Asn	Ser	Gly	Lys	Phe	Asn	Pro
		355					360					365			
Ile	Cys	Lys	Ala	Ser	Gly	Trp	Pro	Leu	Pro	Thr	Asn	Glu	Glu	Met	Thr
	370					375					380				
Leu	Val	Lys	Pro	Asp	Gly	Thr	Val	Leu	His	Pro	Lys	Asp	Phe	Asn	His
385					390					395					400
Thr	Asp	His	Phe	Ser	Val	Ala	Ile	Phe	Thr	Ile	His	Arg	Ile	Leu	Pro
			405						410					415	
Pro	Asp	Ser	Gly	Val	Trp	Val	Cys	Ser	Val	Asn	Thr	Val	Ala	Gly	Met
			420					425					430		
Val	Glu	Lys	Pro	Phe	Asn	Ile	Ser	Val	Lys	Val	Leu	Pro	Lys	Pro	Leu
		435					440					445			
Asn	Ala	Pro	Asn	Val	Ile	Asp	Thr	Gly	His	Asn	Phe	Ala	Val	Ile	Asn
	450					455					460				
Ile	Ser	Ser	Glu	Pro	Tyr	Phe	Gly	Asp	Gly	Pro	Ile	Lys	Ser	Lys	Lys
465					470					475					480
Leu	Leu	Tyr	Lys	Pro	Val	Asn	His	Tyr	Glu	Ala	Trp	Gln	His	Ile	Gln
			485						490					495	
Val	Thr	Asn	Glu	Ile	Val	Thr	Leu	Asn	Tyr	Leu	Glu	Pro	Arg	Thr	Glu
		500						505					510		
Tyr	Glu	Leu	Cys	Val	Gln	Leu	Val	Arg	Arg	Gly	Glu	Gly	Gly	Glu	Gly
	515						520					525			
His	Pro	Gly	Pro	Val	Arg	Arg	Phe	Thr	Thr	Ala	Ser	Ile	Gly	Leu	Pro
	530					535					540				
Pro	Pro	Arg	Gly	Leu	Asn	Leu	Leu	Pro	Lys	Ser	Gln	Thr	Thr	Leu	Asn
545					550					555					560
Leu	Thr	Trp	Gln	Pro	Ser	Ser	Glu	Asp	Asp	Phe	Tyr	Val	Glu	Val	Glu
			565						570					575	
Arg	Arg	Ser	Val	Gln	Lys	Ser	Asp	Gln	Gln	Asn	Ile	Lys	Val	Pro	Gly
			580					585					590		
Asn	Leu	Thr	Ser	Val	Leu	Leu	Asn	Asn	Leu	His	Pro	Arg	Glu	Gln	Tyr
		595					600					605			

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Val Val Arg Ala Arg Val Asn Thr Lys Ala Gln Gly Glu Trp Ser Glu
  610          615          620
Asp Leu Thr Ala Trp Thr Leu Ser Asp Ile Leu Pro Pro Gln Pro Glu
625          630          635          640
Asn Ile Lys Ile Ser Asn Ile Thr His Ser Ser Ala Val Ile Ser Trp
          645          650          655
Thr Ile Leu Asp Gly Tyr Ser Ile Ser Ser Ile Thr Ile Arg Tyr Lys
          660          665          670
Val Gln Gly Lys Asn Glu Asp Gln His Val Asp Val Lys Ile Lys Asn
          675          680          685
Ala Thr Ile Thr Gln Tyr Gln Leu Lys Gly Leu Glu Pro Glu Thr Ala
          690          695          700
Tyr Gln Val Asp Ile Phe Ala Glu Asn Asn Ile Gly Ser Ser Asn Pro
705          710          715          720
Ala Phe Ser His Glu Leu Val Thr Leu Pro Glu Ser Gln Ala Pro Ala
          725          730          735
Asp Leu Gly Gly Gly Lys Met Leu Leu Ile Ala Ile Leu Gly Ser Ala
          740          745          750
Gly Met Thr Cys Leu Thr Val Leu Leu Ala Phe Leu Ile Ile Leu Gln
          755          760          765
Leu Lys Arg Ala Asn Val Gln Arg Arg Met Ala Gln Ala Phe Gln Asn
          770          775          780
Val Arg Glu Glu Pro Ala Val Gln Phe Asn Ser Gly Thr Leu Ala Leu
785          790          795          800
Asn Arg Lys Val Lys Asn Asn Pro Asp Pro Thr Ile Tyr Pro Val Leu
          805          810          815
Asp Trp Asn Asp Ile Lys Phe Gln Asp Val Ile Gly Glu Gly Asn Phe
          820          825          830
Gly Gln Val Leu Lys Ala Arg Ile Lys Lys Asp Gly Leu Arg Met Asp
          835          840          845
Ala Ala Ile Lys Arg Met Lys Glu Tyr Ala Ser Lys Asp Asp His Arg
          850          855          860

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&lt;210&gt; 106

&lt;211&gt; 444

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 106

```

Met Gly Pro Glu Ala Leu Ser Ser Leu Leu Leu Leu Leu Val Ala
  1          5          10          15
Ser Gly Asp Ala Asp Met Lys Gly His Phe Asp Pro Ala Lys Cys Arg
          20          25          30
Tyr Ala Leu Gly Met Gln Asp Arg Thr Ile Pro Asp Ser Asp Ile Ser
          35          40          45
Ala Ser Ser Ser Trp Ser Asp Ser Thr Ala Ala Arg His Ser Arg Leu
          50          55          60
Glu Ser Ser Asp Gly Asp Gly Ala Trp Cys Pro Ala Gly Ser Val Phe
65          70          75          80
Pro Lys Glu Glu Glu Tyr Leu Gln Val Asp Leu Gln Arg Leu His Leu
          85          90          95
Val Ala Leu Val Gly Thr Gln Gly Arg His Ala Gly Gly Leu Gly Lys
          100          105          110
Glu Phe Ser Arg Ser Tyr Arg Leu Arg Tyr Ser Arg Asp Gly Arg Arg
          115          120          125

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Trp Met Gly Trp Lys Asp Arg Trp Gly Gln Glu Val Ile Ser Gly Asn  
 130 135 140  
 Glu Asp Pro Glu Gly Val Val Leu Lys Asp Leu Gly Pro Pro Met Val  
 145 150 155 160  
 Ala Arg Leu Val Arg Phe Tyr Pro Arg Ala Asp Arg Val Met Ser Val  
 165 170 175  
 Cys Leu Arg Val Glu Leu Tyr Gly Cys Leu Trp Arg Asp Gly Leu Leu  
 180 185 190  
 Ser Tyr Thr Ala Pro Val Gly Gln Thr Met Tyr Leu Ser Glu Ala Val  
 195 200 205  
 Tyr Leu Asn Asp Ser Thr Tyr Asp Gly His Thr Val Gly Gly Leu Gln  
 210 215 220  
 Tyr Gly Gly Leu Gly Gln Leu Ala Asp Gly Val Val Gly Leu Asp Asp  
 225 230 235 240  
 Phe Arg Lys Ser Gln Glu Leu Arg Val Trp Pro Gly Tyr Asp Tyr Val  
 245 250 255  
 Gly Trp Ser Asn His Ser Phe Ser Ser Gly Tyr Val Glu Met Glu Phe  
 260 265 270  
 Glu Phe Asp Arg Leu Arg Ala Phe Gln Ala Met Gln Val His Cys Asn  
 275 280 285  
 Asn Met His Thr Leu Gly Ala Arg Leu Pro Gly Gly Val Glu Cys Arg  
 290 295 300  
 Phe Arg Arg Gly Pro Ala Met Ala Trp Glu Gly Glu Pro Met Arg His  
 305 310 315 320  
 Asn Leu Gly Gly Asn Leu Gly Asp Pro Arg Ala Arg Ala Val Ser Val  
 325 330 335  
 Pro Leu Gly Gly Arg Val Ala Arg Phe Leu Gln Cys Arg Phe Cys Pro  
 340 345 350  
 His Leu Pro Arg Thr Ala Ser Pro Ile Met Pro Arg Leu Thr Leu Leu  
 355 360 365  
 Pro Cys Arg Ala Ser Pro Gly Ala Thr Pro Met Leu Cys Leu His Cys  
 370 375 380  
 Pro Gln Gly Gln Ser Gly Met Gly Pro Pro Glu Trp Ile Ser Leu Asp  
 385 390 395 400  
 Leu Asp Ser Ala Ser Arg Arg Ser Leu Ala Arg Ala Ser Leu Gly Arg  
 405 410 415  
 Cys Thr Cys Val Arg Ser Thr Ala Leu Lys Ile Trp Leu Val Leu Ile  
 420 425 430  
 Ser Pro Leu Met Cys Val Arg Asp Thr Leu Cys Trp  
 435 440

&lt;210&gt; 107

&lt;211&gt; 166

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 107

Met Asp Thr Ser Lys Ala Gln Gly Glu Leu Gly Trp Leu Leu Asp Pro  
 1 5 10 15  
 Pro Lys Asp Gly Trp Ser Glu Gln Gln Ile Leu Asn Gly Thr Pro  
 20 25 30  
 Leu Tyr Met Tyr Gln Asp Cys Pro Met Gln Gly Arg Arg Asp Thr Asp  
 35 40 45  
 His Trp Leu Arg Ser Asn Trp Ile Tyr Arg Gly Glu Glu Ala Ser Arg  
 50 55 60

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```

Val His Val Glu Leu Gln Phe Thr Val Arg Asp Cys Lys Ser Phe Pro
65          70          75          80
Gly Gly Ala Gly Pro Leu Gly Cys Lys Glu Thr Phe Asn Leu Leu Tyr
          85          90          95
Met Glu Ser Asp Gln Asp Val Gly Ile Gln Leu Arg Arg Pro Leu Phe
          100        105        110
Gln Lys Val Leu Leu Pro Ser Met Pro Ser Gly Ser Trp Cys Arg Ser
          115        120        125
Leu Val Ala Pro Tyr Trp Val Pro Glu Lys Val Ala Glu Thr Gly Arg
          130        135        140
Gly Cys Arg Gly Arg Ile Leu Lys Arg Ile Trp Arg Leu Lys Ala Gly
145          150        155        160
His Gly Gly Leu Cys Leu
          165

```

<210> 108  
 <211> 90  
 <212> PRT  
 <213> Homo sapiens

```

<400> 108
Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
1          5          10          15
Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
          20          25          30
Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
          35          40          45
Leu Tyr Gln Gly Cys Gln Val Gln Gly Asn Leu Glu Leu Thr Tyr
50          55          60
Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Val Arg Pro Val Gly
65          70          75          80
Asn Pro Ala Arg Pro Cys Leu Gln Leu Gly
          85          90

```

<210> 109  
 <211> 209  
 <212> PRT  
 <213> Homo sapiens

```

<400> 109
Met Met Arg Thr Pro Ser Pro Ile Gly Thr Pro Arg Ile Gly Thr Val
1          5          10          15
Thr Pro Ser Lys Val Ser Arg Ser Pro Arg Thr Cys Val Pro Ala Ala
          20          25          30
Ala His Leu Ile Thr Glu Lys Arg Arg Pro Val Trp Glu His Thr Val
          35          40          45
Ile Leu Gly Ala Phe Pro Cys Pro Pro Ala Pro Tyr Trp Thr His Pro
50          55          60
Gln Arg Met Glu Lys Lys Leu His Ala Val Pro Ala Gly Asn Thr Val
65          70          75          80
Lys Phe Arg Cys Pro Ala Ala Gly Asn Pro Thr Pro Thr Ile Arg Trp
          85          90          95
Leu Lys Asp Gly Gln Ala Phe His Gly Glu Asn Arg Ile Gly Gly Ile
          100        105        110

```

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```

Arg Leu Arg His Gln His Trp Ser Leu Val Met Glu Ser Val Val Pro
   115   120   125
Ser Asp Arg Gly Thr Tyr Thr Cys Leu Val Glu Asn Ala Val Gly Ser
   130   135   140
Ile Arg Tyr Asn Tyr Leu Leu Asp Val Leu Glu Arg Ser Pro His Arg
   145   150   155   160
Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Thr Thr Ala Val Val Gly
   165   170   175
Ser Asp Val Glu Leu Leu Cys Lys Val Tyr Ser Asp Ala Gln Pro His
   180   185   190
Ile Gln Trp Leu Lys His Ile Val Ile Asn Gly Ser Ser Phe Gly Ala
   195   200   205
Asp

```

```

<210> 110
<211> 479
<212> PRT
<213> Homo sapiens

```

```

<400> 110
Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala Leu Leu Ser
  1      5      10      15
Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Lys Leu Lys Asp Pro
  20      25      30
Glu Leu Ser Leu Lys Gly Thr Gln His Ile Met Gln Ala Gly Gln Thr
  35      40      45
Leu His Leu Gln Cys Arg Gly Glu Ala Ala His Lys Trp Ser Leu Pro
  50      55      60
Glu Met Val Ser Lys Glu Ser Glu Arg Leu Ser Ile Thr Lys Ser Ala
  65      70      75      80
Cys Gly Arg Asn Gly Lys Gln Phe Cys Ser Thr Leu Thr Leu Asn Thr
  85      90      95
Ala Gln Ala Asn His Thr Gly Phe Tyr Ser Cys Lys Tyr Leu Ala Val
  100     105     110
Pro Thr Ser Lys Lys Lys Glu Thr Glu Ser Ala Ile Tyr Ile Phe Ile
  115     120     125
Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu
  130     135     140
Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val
  145     150     155     160
Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr
  165     170     175
Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe
  180     185     190
Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu
  195     200     205
Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg
  210     215     220
Gln Thr Asn Thr Ile Ile Asp Val Gln Ile Ser Thr Pro Arg Pro Val
  225     230     235     240
Lys Leu Leu Arg Gly His Thr Leu Val Leu Asn Cys Thr Ala Thr Thr
  245     250     255
Pro Leu Asn Thr Arg Val Gln Met Thr Trp Ser Tyr Pro Asp Glu Lys
  260     265     270

```

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```

Asn Lys Arg Ala Ser Val Arg Arg Arg Ile Asp Gln Ser Asn Ser His
  275      280      285
Ala Asn Ile Phe Tyr Ser Val Leu Thr Ile Asp Lys Met Gln Asn Lys
  290      295      300
Asp Lys Gly Leu Tyr Thr Cys Arg Val Arg Ser Gly Pro Ser Phe Lys
  305      310      315      320
Ser Val Asn Thr Ser Val His Ile Tyr Asp Lys Ala Phe Ile Thr Val
      325      330      335
Lys His Arg Lys Gln Gln Val Leu Glu Thr Val Ala Gly Lys Arg Ser
      340      345      350
Tyr Arg Leu Ser Met Lys Val Lys Ala Phe Pro Ser Pro Glu Val Val
      355      360      365
Trp Leu Lys Asp Gly Leu Pro Ala Thr Glu Lys Ser Ala Arg Tyr Leu
      370      375      380
Thr Arg Gly Tyr Ser Leu Ile Ile Lys Asp Val Thr Glu Glu Asp Ala
  385      390      395      400
Gly Asn Tyr Thr Ile Leu Leu Ser Ile Lys Gln Ser Asn Val Phe Lys
      405      410      415
Asn Leu Thr Ala Thr Leu Ile Val Asn Val Lys Pro Gln Ile Tyr Glu
      420      425      430
Lys Ala Val Ser Ser Phe Pro Asp Pro Ala Leu Tyr Pro Leu Gly Ser
      435      440      445
Arg Gln Ile Leu Thr Cys Thr Ala Tyr Gly Ile Pro Gln Pro Thr Ile
      450      455      460
Lys Trp Phe Trp His Pro Cys Asn His Asn His Ser Glu Ala Arg
  465      470      475

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<210> 111
<211> 217
<212> PRT
<213> Homo sapiens

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<400> 111
Met Gly Thr Ser His Pro Ala Phe Leu Val Leu Gly Cys Leu Leu Thr
  1      5      10      15
Gly Leu Ser Leu Ile Leu Cys Gln Leu Ser Leu Pro Ser Ile Leu Pro
  20      25      30
Asn Glu Asn Glu Lys Val Val Gln Leu Asn Ser Ser Phe Ser Leu Arg
  35      40      45
Cys Phe Gly Glu Ser Glu Val Ser Trp Gln Tyr Pro Met Ser Glu Glu
  50      55      60
Glu Ser Ser Asp Val Glu Ile Arg Asn Glu Glu Asn Asn Ser Gly Leu
  65      70      75      80
Phe Val Thr Val Leu Glu Val Ser Ser Ala Ser Ala Ala His Thr Gly
      85      90      95
Leu Tyr Thr Cys Tyr Tyr Asn His Thr Gln Thr Glu Glu Asn Glu Leu
      100      105      110
Glu Gly Arg His Ile Tyr Ile Tyr Val Pro Asp Pro Asp Val Ala Phe
      115      120      125
Val Pro Leu Gly Met Thr Asp Tyr Leu Val Ile Val Glu Asp Asp Asp
      130      135      140
Ser Ala Ile Ile Pro Cys Arg Thr Thr Asp Pro Glu Thr Pro Val Thr
  145      150      155      160
Leu His Asn Ser Glu Gly Val Val Pro Ala Ser Tyr Asp Ser Arg Gln
      165      170      175

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Gly	Phe	Asn	Gly	Thr	Phe	Thr	Val	Gly	Pro	Tyr	Ile	Cys	Glu	Ala	Thr
			180					185					190		
Val	Lys	Gly	Lys	Lys	Phe	Gln	Thr	Ile	Pro	Phe	Asn	Val	Tyr	Ala	Leu
		195					200					205			
Lys	Gly	Thr	Cys	Ile	Ile	Ser	Phe	Leu							
	210					215									

&lt;210&gt; 112

&lt;211&gt; 798

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 112

Met	Asp	Leu	Ile	Leu	Ile	Asn	Ser	Leu	Pro	Leu	Val	Ser	Asp	Ala	Glu
1				5					10					15	
Thr	Ser	Leu	Thr	Cys	Ile	Ala	Ser	Gly	Trp	Arg	Pro	His	Glu	Pro	Ile
		20						25					30		
Thr	Ile	Gly	Arg	Asp	Phe	Glu	Ala	Leu	Met	Asn	Gln	His	Gln	Asp	Pro
		35				40					45				
Leu	Glu	Val	Thr	Gln	Asp	Val	Thr	Arg	Glu	Trp	Ala	Lys	Lys	Val	Val
	50					55					60				
Trp	Lys	Arg	Glu	Lys	Ala	Ser	Lys	Ile	Asn	Gly	Ala	Tyr	Phe	Cys	Glu
65				70					75					80	
Gly	Arg	Val	Arg	Gly	Glu	Ala	Ile	Arg	Ile	Arg	Thr	Met	Lys	Met	Arg
			85					90					95		
Gln	Gln	Ala	Ser	Phe	Leu	Pro	Ala	Thr	Leu	Thr	Met	Thr	Val	Asp	Lys
		100					105						110		
Gly	Asp	Asn	Val	Asn	Ile	Ser	Phe	Lys	Lys	Val	Leu	Ile	Lys	Glu	Glu
	115					120					125				
Asp	Ala	Val	Ile	Tyr	Lys	Asn	Gly	Ser	Phe	Ile	His	Ser	Val	Pro	Arg
	130					135					140				
His	Glu	Val	Pro	Asp	Ile	Leu	Glu	Val	His	Leu	Pro	His	Ala	Gln	Pro
145				150					155					160	
Gln	Asp	Ala	Gly	Val	Tyr	Ser	Ala	Arg	Tyr	Ile	Gly	Gly	Asn	Leu	Phe
			165					170					175		
Thr	Ser	Ala	Phe	Thr	Arg	Leu	Ile	Val	Arg	Arg	Cys	Glu	Ala	Gln	Lys
		180					185						190		
Trp	Gly	Pro	Glu	Cys	Asn	His	Leu	Cys	Thr	Ala	Cys	Met	Asn	Asn	Gly
	195					200						205			
Val	Cys	His	Glu	Asp	Thr	Gly	Glu	Cys	Ile	Cys	Pro	Pro	Gly	Phe	Met
	210				215						220				
Gly	Arg	Thr	Cys	Glu	Lys	Ala	Cys	Glu	Leu	His	Thr	Phe	Gly	Arg	Thr
225				230					235					240	
Cys	Lys	Glu	Arg	Cys	Ser	Gly	Gln	Glu	Gly	Cys	Lys	Ser	Tyr	Val	Phe
			245					250					255		
Cys	Leu	Pro	Asp	Pro	Tyr	Gly	Cys	Ser	Cys	Ala	Thr	Gly	Trp	Lys	Gly
		260					265						270		
Leu	Gln	Cys	Asn	Glu	Gly	Ile	Gln	Arg	Met	Thr	Pro	Lys	Ile	Val	Asp
	275					280						285			
Leu	Pro	Asp	His	Ile	Glu	Val	Asn	Ser	Gly	Lys	Phe	Asn	Pro	Ile	Cys
	290				295						300				
Lys	Ala	Ser	Gly	Trp	Pro	Leu	Pro	Thr	Asn	Glu	Glu	Met	Thr	Leu	Val
305				310					315					320	
Lys	Pro	Asp	Gly	Thr	Val	Leu	His	Pro	Lys	Asp	Phe	Asn	His	Thr	Asp
			325					330					335		



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His	Phe	Ser	Val	Ala	Ile	Phe	Thr	Ile	His	Arg	Ile	Leu	Pro	Pro	Asp
			340					345					350		
Ser	Gly	Val	Trp	Val	Cys	Ser	Val	Asn	Thr	Val	Ala	Gly	Met	Val	Glu
		355					360					365			
Lys	Pro	Phe	Asn	Ile	Ser	Val	Lys	Val	Leu	Pro	Lys	Pro	Leu	Asn	Ala
		370				375					380				
Pro	Asn	Val	Ile	Asp	Thr	Gly	His	Asn	Phe	Ala	Val	Ile	Asn	Ile	Ser
385				390					395						400
Ser	Glu	Pro	Tyr	Phe	Gly	Asp	Gly	Pro	Ile	Lys	Ser	Lys	Lys	Leu	Leu
			405						410					415	
Tyr	Lys	Pro	Val	Asn	His	Tyr	Glu	Ala	Trp	Gln	His	Ile	Gln	Val	Thr
			420					425					430		
Asn	Glu	Ile	Val	Thr	Leu	Asn	Tyr	Leu	Glu	Pro	Arg	Thr	Glu	Tyr	Glu
		435					440					445			
Leu	Cys	Val	Gln	Leu	Val	Arg	Arg	Gly	Glu	Gly	Gly	Glu	Gly	His	Pro
		450				455					460				
Gly	Pro	Val	Arg	Arg	Phe	Thr	Thr	Ala	Ser	Ile	Gly	Leu	Pro	Pro	Pro
465				470					475						480
Arg	Gly	Leu	Asn	Leu	Leu	Pro	Lys	Ser	Gln	Thr	Thr	Leu	Asn	Leu	Thr
			485						490					495	
Trp	Gln	Pro	Ser	Ser	Glu	Asp	Asp	Phe	Tyr	Val	Glu	Val	Glu	Arg	Arg
		500						505					510		
Ser	Val	Gln	Lys	Ser	Asp	Gln	Gln	Asn	Ile	Lys	Val	Pro	Gly	Asn	Leu
		515					520					525			
Thr	Ser	Val	Leu	Leu	Asn	Asn	Leu	His	Pro	Arg	Glu	Gln	Tyr	Val	Val
		530				535					540				
Arg	Ala	Arg	Val	Asn	Thr	Lys	Ala	Gln	Gly	Glu	Trp	Ser	Glu	Asp	Leu
545				550					555						560
Thr	Ala	Trp	Thr	Leu	Ser	Asp	Ile	Leu	Pro	Pro	Gln	Pro	Glu	Asn	Ile
			565						570					575	
Lys	Ile	Ser	Asn	Ile	Thr	His	Ser	Ser	Ala	Val	Ile	Ser	Trp	Thr	Ile
			580					585					590		
Leu	Asp	Gly	Tyr	Ser	Ile	Ser	Ser	Ile	Thr	Ile	Arg	Tyr	Lys	Val	Gln
		595					600					605			
Gly	Lys	Asn	Glu	Asp	Gln	His	Val	Asp	Val	Lys	Ile	Lys	Asn	Ala	Thr
		610				615					620				
Ile	Thr	Gln	Tyr	Gln	Leu	Lys	Gly	Leu	Glu	Pro	Glu	Thr	Ala	Tyr	Gln
625				630					635						640
Val	Asp	Ile	Phe	Ala	Glu	Asn	Asn	Ile	Gly	Ser	Ser	Asn	Pro	Ala	Phe
			645						650					655	
Ser	His	Glu	Leu	Val	Thr	Leu	Pro	Glu	Ser	Gln	Ala	Pro	Ala	Asp	Leu
			660					665				670			
Gly	Gly	Gly	Lys	Met	Leu	Leu	Ile	Ala	Ile	Leu	Gly	Ser	Ala	Gly	Met
		675					680					685			
Thr	Cys	Leu	Thr	Val	Leu	Leu	Ala	Phe	Leu	Ile	Ile	Leu	Gln	Leu	Lys
		690				695					700				
Arg	Ala	Asn	Val	Gln	Arg	Arg	Met	Ala	Gln	Ala	Phe	Gln	Asn	Val	Arg
705				710					715						720
Glu	Glu	Pro	Ala	Val	Gln	Phe	Asn	Ser	Gly	Thr	Leu	Ala	Leu	Asn	Arg
			725						730					735	
Lys	Val	Lys	Asn	Asn	Pro	Asp	Pro	Thr	Ile	Tyr	Pro	Val	Leu	Asp	Trp
			740					745					750		
Asn	Asp	Ile	Lys	Phe	Gln	Asp	Val	Ile	Gly	Glu	Gly	Asn	Phe	Gly	Gln
		755				760						765			
Val	Leu	Lys	Ala	Arg	Ile	Lys	Lys	Asp	Gly	Leu	Arg	Met	Asp	Ala	Ala
		770				775					780				

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Ile Lys Arg Met Lys Glu Tyr Ala Ser Lys Asp Asp His Arg  
 785 790 795

<210> 113  
 <211> 786  
 <212> PRT  
 <213> Homo sapiens

<400> 113  
 Met Val Trp Arg Val Pro Pro Phe Leu Leu Pro Ile Leu Phe Leu Ala  
 1 5 10 15  
 Ser His Val Gly Ala Ala Val Asp Leu Thr Leu Leu Ala Asn Leu Arg  
 20 25 30  
 Leu Thr Asp Pro Gln Arg Phe Phe Leu Thr Cys Val Ser Gly Glu Ala  
 35 40 45  
 Gly Ala Gly Arg Gly Ser Asp Ala Trp Gly Pro Pro Leu Leu Glu  
 50 55 60  
 Lys Asp Asp Arg Ile Val Arg Thr Pro Pro Gly Pro Pro Leu Arg Leu  
 65 70 75 80  
 Ala Arg Asn Gly Ser His Gln Val Thr Leu Arg Gly Phe Ser Lys Pro  
 85 90 95  
 Ser Asp Leu Val Gly Val Phe Ser Cys Val Gly Gly Ala Gly Ala Arg  
 100 105 110  
 Arg Thr Arg Val Ile Tyr Val His Asn Ser Pro Gly Ala His Leu Leu  
 115 120 125  
 Pro Asp Lys Val Thr His Thr Val Asn Lys Gly Asp Thr Ala Val Leu  
 130 135 140  
 Ser Ala Arg Val His Lys Glu Lys Gln Thr Asp Val Ile Trp Lys Ser  
 145 150 155 160  
 Asn Gly Ser Tyr Phe Tyr Thr Leu Asp Trp His Glu Ala Gln Asp Gly  
 165 170 175  
 Arg Phe Leu Leu Gln Leu Pro Asn Val Gln Pro Pro Ser Ser Gly Ile  
 180 185 190  
 Tyr Ser Ala Thr Tyr Leu Glu Ala Ser Pro Leu Gly Ser Ala Phe Phe  
 195 200 205  
 Arg Leu Ile Val Arg Gly Cys Gly Ala Gly Arg Trp Gly Pro Gly Cys  
 210 215 220  
 Thr Lys Glu Cys Pro Gly Cys Leu His Gly Gly Val Cys His Asp His  
 225 230 235 240  
 Asp Gly Glu Cys Val Cys Pro Pro Gly Phe Thr Gly Thr Arg Cys Glu  
 245 250 255  
 Gln Ala Cys Arg Glu Gly Arg Phe Gly Gln Ser Cys Gln Glu Gln Cys  
 260 265 270  
 Pro Gly Ile Ser Gly Cys Arg Gly Leu Thr Phe Cys Leu Pro Asp Pro  
 275 280 285  
 Tyr Gly Cys Ser Cys Gly Ser Gly Trp Arg Gly Ser Gln Cys Gln Glu  
 290 295 300  
 Ala Cys Ala Pro Gly His Phe Gly Ala Asp Cys Arg Leu Gln Cys Gln  
 305 310 315 320  
 Cys Gln Asn Gly Gly Thr Cys Asp Arg Phe Ser Gly Cys Val Cys Pro  
 325 330 335  
 Ser Gly Trp His Gly Val His Cys Glu Lys Ser Asp Arg Ile Pro Gln  
 340 345 350  
 Ile Leu Asn Met Ala Ser Glu Leu Glu Phe Asn Leu Glu Thr Met Pro  
 355 360 365

Arg	Ile	Asn	Cys	Ala	Ala	Ala	Gly	Asn	Pro	Phe	Pro	Val	Arg	Gly	Ser
Ile	Glu	Leu	Arg	Lys	Pro	Asp	Gly	Thr	Val	Leu	Leu	Ser	Thr	Lys	Ala
370	385			390					395					400	
Ile	Val	Glu	Pro	Glu	Lys	Thr	Thr	Ala	Glu	Phe	Glu	Val	Pro	Arg	Leu
				405					410					415	
Val	Leu	Ala	Asp	Ser	Gly	Phe	Trp	Glu	Cys	Arg	Val	Ser	Thr	Ser	Gly
				420				425					430		
Gly	Gln	Asp	Ser	Arg	Arg	Phe	Lys	Val	Asn	Val	Lys	Val	Pro	Pro	Val
				435			440					445			
Pro	Leu	Ala	Ala	Pro	Arg	Leu	Leu	Thr	Lys	Gln	Ser	Arg	Gln	Leu	Val
						455					460				
Val	Ser	Pro	Leu	Val	Ser	Phe	Ser	Gly	Asp	Gly	Pro	Ile	Ser	Thr	Val
465					470				475						480
Arg	Leu	His	Tyr	Arg	Pro	Gln	Asp	Ser	Thr	Met	Asp	Trp	Ser	Thr	Ile
				485					490					495	
Val	Val	Asp	Pro	Ser	Glu	Asn	Val	Thr	Leu	Met	Asn	Leu	Arg	Pro	Lys
				500				505					510		
Thr	Gly	Tyr	Ser	Val	Arg	Val	Gln	Leu	Ser	Arg	Pro	Gly	Glu	Gly	Gly
				515			520					525			
Glu	Gly	Ala	Trp	Gly	Pro	Pro	Thr	Leu	Met	Thr	Thr	Asp	Cys	Pro	Glu
						535					540				
Pro	Leu	Leu	Gln	Pro	Trp	Leu	Glu	Gly	Trp	His	Val	Glu	Gly	Thr	Asp
545					550				555						560
Arg	Leu	Arg	Val	Ser	Trp	Ser	Leu	Pro	Leu	Val	Pro	Gly	Pro	Leu	Val
				565					570					575	
Gly	Asp	Gly	Phe	Leu	Leu	Arg	Leu	Trp	Asp	Gly	Thr	Arg	Gly	Gln	Glu
				580				585					590		
Arg	Arg	Glu	Asn	Val	Ser	Ser	Pro	Gln	Ala	Arg	Thr	Ala	Leu	Leu	Thr
				595			600					605			
Gly	Leu	Thr	Pro	Gly	Thr	His	Tyr	Gln	Leu	Asp	Val	Gln	Leu	Tyr	His
						615					620				
Cys	Thr	Leu	Leu	Gly	Pro	Ala	Ser	Pro	Pro	Ala	His	Val	Leu	Leu	Pro
625					630				635						640
Pro	Ser	Gly	Pro	Pro	Ala	Pro	Arg	His	Leu	His	Ala	Gln	Ala	Leu	Ser
				645					650					655	
Asp	Ser	Glu	Ile	Gln	Leu	Thr	Trp	Lys	His	Pro	Glu	Ala	Leu	Pro	Gly
				660				665					670		
Pro	Ile	Ser	Lys	Tyr	Val	Val	Glu	Val	Gln	Val	Ala	Gly	Gly	Ala	Gly
						680						685			
Asp	Pro	Leu	Trp	Ile	Asp	Val	Asp	Arg	Pro	Glu	Glu	Thr	Ser	Thr	Ile
						695					700				
Ile	Arg	Gly	Leu	Asn	Ala	Ser	Thr	Arg	Tyr	Leu	Phe	Arg	Met	Arg	Ala
705					710				715						720
Ser	Ile	Gln	Gly	Leu	Gly	Asp	Trp	Ser	Asn	Thr	Val	Glu	Glu	Ser	Thr
		</													

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<210> 114
<211> 984
<212> DNA
<213> Homo Sapiens
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<220>  
<221> CDS  
<222> (37) ... (897)  
<223> SR005 A11
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<400> 114																	
tgccccccacc	cccttaggcc	cgaggggatca	ggagct	atg	gga	cca	gag	gcc	ctg								54
				Met	Gly	Pro	Glu	Ala	Leu								
				1				5									
tca	tct	tta	ctg	ctg	ctg	ctc	ttg	gtg	gca	agt	gga	gat	gct	gac	atg		102
Ser	Ser	Leu	Leu	Leu	Leu	Leu	Leu	Val	Ala	Ser	Gly	Asp	Ala	Asp	Met		
			10					15					20				
aag	gga	cat	ttt	gat	cct	gcc	aag	tgc	cgc	tat	gcc	ctg	ggc	atg	cag		150
Lys	Gly	His	Phe	Asp	Pro	Ala	Lys	Cys	Arg	Tyr	Ala	Leu	Gly	Met	Gln		
		25					30					35					
gac	cgg	acc	atc	cca	gac	agt	gac	atc	tct	gct	tcc	agc	tcc	tgg	tca		198
Asp	Arg	Thr	Ile	Pro	Asp	Ser	Asp	Ile	Ser	Ala	Ser	Ser	Ser	Trp	Ser		
	40					45					50						
gat	tcc	act	gcc	gcc	cgc	cac	agc	agg	ttg	gag	agc	agt	gac	ggg	gat		246
Asp	Ser	Thr	Ala	Ala	Arg	His	Ser	Arg	Leu	Glu	Ser	Ser	Asp	Gly	Asp		
	55				60					65					70		
ggg	gcc	tgg	tgc	ccc	gca	ggg	tcg	gtg	ttt	ccc	aag	gag	gag	gag	tac		294
Gly	Ala	Trp	Cys	Pro	Ala	Gly	Ser	Val	Phe	Pro	Lys	Glu	Glu	Glu	Tyr		
				75					80					85			
ttg	cag	gtg	gat	cta	caa	cga	ctg	cac	ctg	gtg	gct	ctg	gtg	ggc	acc		342
Leu	Gln	Val	Asp	Leu	Gln	Arg	Leu	His	Leu	Val	Ala	Leu	Val	Gly	Thr		
			90					95					100				
cag	gga	cgg	cat	gcc	ggg	ggc	ctg	ggc	aag	gag	ttc	tcc	cgg	agc	tac		390
Gln	Gly	Arg	His	Ala	Gly	Gly	Leu	Gly	Lys	Glu	Phe	Ser	Arg	Ser	Tyr		
		105					110					115					
cgg	ctg	cgt	tac	tcc	cgg	gat	ggt	cgc	cgc	tgg	atg	ggc	tgg	aag	gac		438
Arg	Leu	Arg	Tyr	Ser	Arg	Asp	Gly	Arg	Arg	Trp	Met	Gly	Trp	Lys	Asp		
	120					125					130						
cgc	tgg	ggt	cag	gag	gtg	atc	tca	ggc	aat	gag	gac	cct	gag	gga	gtg		486
Arg	Trp	Gly	Gln	Glu	Val	Ile	Ser	Gly	Asn	Glu	Asp	Pro	Glu	Gly	Val		
					140					145					150		
gtg	ctg	aag	gac	ctt	ggg	ccc	ccc	atg	gtt	gcc	cga	ctg	gtt	cgc	ttc		534
Val	Leu	Lys	Asp	Leu	Gly	Pro	Pro	Met	Val	Ala	Arg	Leu	Val	Arg	Phe		
				155					160					165			
tac	ccc	cgg	gct	gac	cgg	gtc	atg	agc	gtc	tgt	ctg	cgg	gta	gag	ctc		582

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Tyr Pro Arg Ala Asp Arg Val Met Ser Val Cys Leu Arg Val Glu Leu
      170                      175                      180

tat ggc tgc ctc tgg agg gat gga ctc ctg tct tac acc gcc cct gtg   630
Tyr Gly Cys Leu Trp Arg Asp Gly Leu Leu Ser Tyr Thr Ala Pro Val
      185                      190                      195

ggg cag aca atg tat tta tct gag gcc gtg tac ctc aac gac tcc acc   678
Gly Gln Thr Met Tyr Leu Ser Glu Ala Val Tyr Leu Asn Asp Ser Thr
      200                      205                      210

tat gac gga cat acc gtg ggc gga ctg cag tat ggg ggt ctg ggc cag   726
Tyr Asp Gly His Thr Val Gly Gly Leu Gln Tyr Gly Gly Leu Gly Gln
      215                      220                      225

ctg gca gat ggt gtg gtg ggg ctg gat gac ttt agg aag agt cag gag   774
Leu Ala Asp Gly Val Val Gly Leu Asp Asp Phe Arg Lys Ser Gln Glu
      235                      240                      245

ctg cgg gtc tgg cca ggc tat gac tat gtg gga tgg agc aac cac agc   822
Leu Arg Val Trp Pro Gly Tyr Asp Tyr Val Gly Trp Ser Asn His Ser
      250                      255                      260

ttc tcc agt ggc tat gtg gag atg gag ttt gag ttt gac cgg ctg agg   870
Phe Ser Ser Gly Tyr Val Glu Met Glu Phe Glu Phe Asp Arg Leu Arg
      265                      270                      275

gcc ttc cag gct atg cag atg tgg tga acaattcctc tccggcactg   917
Ala Phe Gln Ala Met Gln Met Trp *
      280                      285

ggaggcacct tcccgccagc cccctggtgg ccgcctggcc cacctccac caacttcagc 977
agcttgg                                     984

<210> 115
<211> 286
<212> PRT
<213> Homo Sapiens

<400> 115
Met Gly Pro Glu Ala Leu Ser Ser Leu Leu Leu Leu Leu Leu Val Ala
  1      5      10      15
Ser Gly Asp Ala Asp Met Lys Gly His Phe Asp Pro Ala Lys Cys Arg
  20      25      30
Tyr Ala Leu Gly Met Gln Asp Arg Thr Ile Pro Asp Ser Asp Ile Ser
  35      40      45
Ala Ser Ser Ser Trp Ser Asp Ser Thr Ala Ala Arg His Ser Arg Leu
  50      55      60
Glu Ser Ser Asp Gly Asp Gly Ala Trp Cys Pro Ala Gly Ser Val Phe
  65      70      75      80
Pro Lys Glu Glu Glu Tyr Leu Gln Val Asp Leu Gln Arg Leu His Leu
  85      90      95
Val Ala Leu Val Gly Thr Gln Gly Arg His Ala Gly Gly Leu Gly Lys
  100     105     110
Glu Phe Ser Arg Ser Tyr Arg Leu Arg Tyr Ser Arg Asp Gly Arg Arg
  115     120     125

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Trp Met Gly Trp Lys Asp Arg Trp Gly Gln Glu Val Ile Ser Gly Asn  
 130 135 140  
 Glu Asp Pro Glu Gly Val Val Leu Lys Asp Leu Gly Pro Pro Met Val  
 145 150 155 160  
 Ala Arg Leu Val Arg Phe Tyr Pro Arg Ala Asp Arg Val Met Ser Val  
 165 170 175  
 Cys Leu Arg Val Glu Leu Tyr Gly Cys Leu Trp Arg Asp Gly Leu Leu  
 180 185 190  
 Ser Tyr Thr Ala Pro Val Gly Gln Thr Met Tyr Leu Ser Glu Ala Val  
 195 200 205  
 Tyr Leu Asn Asp Ser Thr Tyr Asp Gly His Thr Val Gly Gly Leu Gln  
 210 215 220  
 Tyr Gly Gly Leu Gly Gln Leu Ala Asp Gly Val Val Gly Leu Asp Asp  
 225 230 235 240  
 Phe Arg Lys Ser Gln Glu Leu Arg Val Trp Pro Gly Tyr Asp Tyr Val  
 245 250 255  
 Gly Trp Ser Asn His Ser Phe Ser Ser Gly Tyr Val Glu Met Glu Phe  
 260 265 270  
 Glu Phe Asp Arg Leu Arg Ala Phe Gln Ala Met Gln Met Trp  
 275 280 285

&lt;210&gt; 116

&lt;211&gt; 788

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (37)...(768)

&lt;400&gt; 116

tgccccacc cccttaggcc cgagggatca ggagct atg gga cca gag gcc ctg 54  
 Met Gly Pro Glu Ala Leu  
 1 5  
  
 tca tct tta ctg ctg ctg ctc ttg gtg gca agt gga gat gct gac atg 102  
 Ser Ser Leu Leu Leu Leu Leu Val Ala Ser Gly Asp Ala Asp Met  
 10 15 20  
  
 aag gga cat ttt gat cct gcc aag tgc cgc tat gcc ctg ggc atg cag 150  
 Lys Gly His Phe Asp Pro Ala Lys Cys Arg Tyr Ala Leu Gly Met Gln  
 25 30 35  
  
 gac cgg acc atc cca gac agt gac atc tct gct tcc agc tcc tgg tca 198  
 Asp Arg Thr Ile Pro Asp Ser Asp Ile Ser Ala Ser Ser Ser Trp Ser  
 40 45 50  
  
 gat tcc act gcc gcc cgc cac agc agg ttg gag agc agt gac ggg gat 246  
 Asp Ser Thr Ala Ala Arg His Ser Arg Leu Glu Ser Ser Asp Gly Asp  
 55 60 65 70  
  
 ggg gcc tgg tgc ccc gca ggg tcg gtg ttt ccc aag gag gag gag tac 294  
 Gly Ala Trp Cys Pro Ala Gly Ser Val Phe Pro Lys Glu Glu Glu Tyr  
 75 80 85

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ttg cag gtg gat cta caa cga ctg cac ctg gtg gct ctg gtg ggc acc 342
Leu Gln Val Asp Leu Gln Arg Leu His Leu Val Ala Leu Val Gly Thr
          90                      95                      100

cag gga cgg cat gcc ggg ggc ctg ggc aag gag ttc tcc cgg agc tac 390
Gln Gly Arg His Ala Gly Gly Leu Gly Lys Glu Phe Ser Arg Ser Tyr
          105                      110                      115

cgg ctg cgt tac tcc cgg gat ggt cgc cgc tgg atg ggc tgg aag gac 438
Arg Leu Arg Tyr Ser Arg Asp Gly Arg Arg Trp Met Gly Trp Lys Asp
          120                      125                      130

cgc tgg ggt cag gag gtg atc tca ggc aat gag gac cct gag gga gtg 486
Arg Trp Gly Gln Glu Val Ile Ser Gly Asn Glu Asp Pro Glu Gly Val
          135                      140                      145                      150

gtg ctg aag gac ctt ggg ccc ccc atg gtt gcc cga ctg gtt cgc ttc 534
Val Leu Lys Asp Leu Gly Pro Pro Met Val Ala Arg Leu Val Arg Phe
          155                      160                      165

tac ccc cgg gct gac cgg gtc atg agc gtc tgt ctg cgg gta gag ctc 582
Tyr Pro Arg Ala Asp Arg Val Met Ser Val Cys Leu Arg Val Glu Leu
          170                      175                      180

tat ggc tgc ctc tgg agg gac tgc agt atg ggg gtc tgg gcc agc tgg 630
Tyr Gly Cys Leu Trp Arg Asp Cys Ser Met Gly Val Trp Ala Ser Trp
          185                      190                      195

cag atg gtg tgg tgg ggc tgg atg act tta gga aga gtc agg agc tgc 678
Gln Met Val Trp Trp Gly Trp Met Thr Leu Gly Arg Val Arg Ser Cys
          200                      205                      210

ggg tct ggc cag gct atg act atg tgg gat gga gca acc aca gct tct 726
Gly Ser Gly Gln Ala Met Thr Met Trp Asp Gly Ala Thr Thr Ala Ser
          215                      220                      225                      230

cca gtg gct atg tgg aga tgg agt ttg agt ttg acc ggc tga 768
Pro Val Ala Met Trp Arg Trp Ser Leu Ser Leu Thr Gly *
          235                      240

gggccttcca ggctatgcag 788

<210> 117
<211> 243
<212> PRT
<213> Homo Sapiens

<400> 117
Met Gly Pro Glu Ala Leu Ser Ser Leu Leu Leu Leu Leu Val Ala
 1          5          10          15
Ser Gly Asp Ala Asp Met Lys Gly His Phe Asp Pro Ala Lys Cys Arg
 20          25          30
Tyr Ala Leu Gly Met Gln Asp Arg Thr Ile Pro Asp Ser Asp Ile Ser
 35          40          45
Ala Ser Ser Ser Trp Ser Asp Ser Thr Ala Ala Arg His Ser Arg Leu
 50          55          60

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- 54 -

Glu Ser Ser Asp Gly Asp Gly Ala Trp Cys Pro Ala Gly Ser Val Phe  
 65 70 75 80  
 Pro Lys Glu Glu Glu Tyr Leu Gln Val Asp Leu Gln Arg Leu His Leu  
 85 90 95  
 Val Ala Leu Val Gly Thr Gln Gly Arg His Ala Gly Gly Leu Gly Lys  
 100 105 110  
 Glu Phe Ser Arg Ser Tyr Arg Leu Arg Tyr Ser Arg Asp Gly Arg Arg  
 115 120 125  
 Trp Met Gly Trp Lys Asp Arg Trp Gly Gln Glu Val Ile Ser Gly Asn  
 130 135 140  
 Glu Asp Pro Glu Gly Val Val Leu Lys Asp Leu Gly Pro Pro Met Val  
 145 150 155 160  
 Ala Arg Leu Val Arg Phe Tyr Pro Arg Ala Asp Arg Val Met Ser Val  
 165 170 175  
 Cys Leu Arg Val Glu Leu Tyr Gly Cys Leu Trp Arg Asp Cys Ser Met  
 180 185 190  
 Gly Val Trp Ala Ser Trp Gln Met Val Trp Trp Gly Trp Met Thr Leu  
 195 200 205  
 Gly Arg Val Arg Ser Cys Gly Ser Gly Gln Ala Met Thr Met Trp Asp  
 210 215 220  
 Gly Ala Thr Thr Ala Ser Pro Val Ala Met Trp Arg Trp Ser Leu Ser  
 225 230 235 240  
 Leu Thr Gly

<210> 118  
 <211> 878  
 <212> DNA  
 <213> Homo Sapiens

<220>  
 <221> CDS  
 <222> (9)...(695)

<400> 118  
 gaactggg atg tgg agc tgg aag tgc ctc ctc ttc tgg gct gtg ctg gtc 50  
 Met Trp Ser Trp Lys Cys Leu Leu Phe Trp Ala Val Leu Val  
 1 5 10  
 aca gcc aca ctc tgc acc gct agg ccg tcc ccg acc ttg cct gaa caa 98  
 Thr Ala Thr Leu Cys Thr Ala Arg Pro Ser Pro Thr Leu Pro Glu Gln  
 15 20 25 30  
 gat gct ctc ccc tcc tcg gag gat gat gat gat gat gat gac tcc tct 146  
 Asp Ala Leu Pro Ser Ser Glu Asp Asp Asp Asp Asp Asp Ser Ser  
 35 40 45  
 tca gag gag aaa gaa aca gat aac acc aaa cca aac ccc gta gct cca 194  
 Ser Glu Glu Lys Glu Thr Asp Asn Thr Lys Pro Asn Pro Val Ala Pro  
 50 55 60  
 tat tgg aca tcc cca gaa aag atg gaa aag aaa ttg cat gca gtg ccg 242  
 Tyr Trp Thr Ser Pro Glu Lys Met Glu Lys Lys Leu His Ala Val Pro  
 65 70 75



- 55 -

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gct gcc aag aca gtg aag ttc aaa tgc cct tcc agt ggg acc cca aac 290
Ala Ala Lys Thr Val Lys Phe Lys Cys Pro Ser Ser Gly Thr Pro Asn
      80                      85                      90

ccc aca ctg cgc tgg ttg aaa aat ggc aaa gaa ttc aaa cct gac cac 338
Pro Thr Leu Arg Trp Leu Lys Asn Gly Lys Glu Phe Lys Pro Asp His
      95                      100                      105                      110

aga att gga ggc tac aag gtc cgt tat gcc acc tgg agc atc ata atg 386
Arg Ile Gly Gly Tyr Lys Val Arg Tyr Ala Thr Trp Ser Ile Ile Met
                        115                      120                      125

gac tct gtg gtg ccc tct gac aag ggc aac tac acc tgc att gtg gag 434
Asp Ser Val Val Pro Ser Asp Lys Gly Asn Tyr Thr Cys Ile Val Glu
                        130                      135                      140

aat gag tac ggc agc atc aac cac aca tac cag ctg gat gtc gtg gag 482
Asn Glu Tyr Gly Ser Ile Asn His Thr Tyr Gln Leu Asp Val Val Glu
                        145                      150                      155

cgg tcc cct cac cgg ccc atc ctg caa gca ggg ttg ccc gcc aac aaa 530
Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Lys
      160                      165                      170

aca gtg gcc ctg ggt agc aac gtg gag ttc atg tgt aag gtg tac agt 578
Thr Val Ala Leu Gly Ser Asn Val Glu Phe Met Cys Lys Val Tyr Ser
      175                      180                      185                      190

gac ccg cag ccg cac atc cag tgg cta aag cac atc gag gtg aat ggg 626
Asp Pro Gln Pro His Ile Gln Trp Leu Lys His Ile Glu Val Asn Gly
                        195                      200                      205

agc aag att ggc cca gac aac ctg cct tat gtc cag atc ttg aag ccc 674
Ser Lys Ile Gly Pro Asp Asn Leu Pro Tyr Val Gln Ile Leu Lys Pro
      210                      215                      220

tgg aag aga ggc cgg cag tga tgacctcgcc cctgtacctg gagatcatca 725
Trp Lys Arg Gly Arg Gln *
      225

tctattgcac aggggccttc ctcatctcct gcatgggtggg gtgggtcatc gtctacaaga 785
tgaagagtgg taccaagaag agtgacttcc acagccagat ggctgtgcac aagctggcca 845
agagcatccc tctgcgcaga caggtaacag aaa 878

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&lt;210&gt; 119

&lt;211&gt; 228

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 119

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Met Trp Ser Trp Lys Cys Leu Leu Phe Trp Ala Val Leu Val Thr Ala
1      5      10      15
Thr Leu Cys Thr Ala Arg Pro Ser Pro Thr Leu Pro Glu Gln Asp Ala
      20      25      30
Leu Pro Ser Ser Glu Asp Asp Asp Asp Asp Ser Ser Ser Glu
      35      40      45

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- 56 -

Glu Lys Glu Thr Asp Asn Thr Lys Pro Asn Pro Val Ala Pro Tyr Trp  
     50                    55                    60  
 Thr Ser Pro Glu Lys Met Glu Lys Lys Leu His Ala Val Pro Ala Ala  
 65                    70                    75                    80  
 Lys Thr Val Lys Phe Lys Cys Pro Ser Ser Gly Thr Pro Asn Pro Thr  
                     85                    90                    95  
 Leu Arg Trp Leu Lys Asn Gly Lys Glu Phe Lys Pro Asp His Arg Ile  
                     100                    105                    110  
 Gly Gly Tyr Lys Val Arg Tyr Ala Thr Trp Ser Ile Ile Met Asp Ser  
                     115                    120                    125  
 Val Val Pro Ser Asp Lys Gly Asn Tyr Thr Cys Ile Val Glu Asn Glu  
 130                    135                    140  
 Tyr Gly Ser Ile Asn His Thr Tyr Gln Leu Asp Val Val Glu Arg Ser  
 145                    150                    155                    160  
 Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Lys Thr Val  
                     165                    170                    175  
 Ala Leu Gly Ser Asn Val Glu Phe Met Cys Lys Val Tyr Ser Asp Pro  
                     180                    185                    190  
 Gln Pro His Ile Gln Trp Leu Lys His Ile Glu Val Asn Gly Ser Lys  
                     195                    200                    205  
 Ile Gly Pro Asp Asn Leu Pro Tyr Val Gln Ile Leu Lys Pro Trp Lys  
                     210                    215                    220  
 Arg Gly Arg Gln  
 225

&lt;210&gt; 120

&lt;211&gt; 1775

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (26)...(1366)

&lt;400&gt; 120

ggtccctgag agctgtgaga aggag atg cgg ctg ctg ctg gcc ctg ttg ggg 52  
                                     Met Arg Leu Leu Leu Ala Leu Leu Gly  
   1                                    5  
  
 gtc ctg ctg agt gtg cct ggg cct cca gtc ttg tcc ctg gag gcc tct 100  
 Val Leu Leu Ser Val Pro Gly Pro Pro Val Leu Ser Leu Glu Ala Ser  
 10                                    15                                    20                                    25  
  
 gag gaa gtg gag ctt gag ccc tgc ctg gct ccc agc ctg gag cag caa 148  
 Glu Glu Val Glu Leu Glu Pro Cys Leu Ala Pro Ser Leu Glu Gln Gln  
                                     30                                    35                                    40  
  
 gag cag gag ctg aca gta gcc ctt ggg cag cct gtg cgt ctg tgc tgt 196  
 Glu Gln Glu Leu Thr Val Ala Leu Gly Gln Pro Val Arg Leu Cys Cys  
                                     45                                    50                                    55  
  
 ggg cgg gct gag cgt ggt ggc cac tgg tac aag gag ggc agt cgc ctg 244  
 Gly Arg Ala Glu Arg Gly Gly His Trp Tyr Lys Glu Gly Ser Arg Leu  
                                     60                                    65                                    70

- 57 -

gca cct gct ggc cgt gta cgg ggc tgg agg ggc cgc cta gag att gcc	292
Ala Pro Ala Gly Arg Val Arg Gly Trp Arg Gly Arg Leu Glu Ile Ala	
75 80 85	
agc ttc cta cct gag gat gct ggc cgc tac ctc tgc ctg gca cga ggc	340
Ser Phe Leu Pro Glu Asp Ala Gly Arg Tyr Leu Cys Leu Ala Arg Gly	
90 95 100 105	
tcc atg atc gtc ctg cag aat ctc acc ttg att aca ggt gac tcc ttg	388
Ser Met Ile Val Leu Gln Asn Leu Thr Leu Ile Thr Gly Asp Ser Leu	
110 115 120	
acc tcc agc aac gat gat gag gac ccc aag tcc cat agg gac ccc tcg	436
Thr Ser Ser Asn Asp Asp Glu Asp Pro Lys Ser His Arg Asp Pro Ser	
125 130 135	
aat agg cac agt tac ccc cag caa gca ccc tac tgg aca cac ccc cag	484
Asn Arg His Ser Tyr Pro Gln Gln Ala Pro Tyr Trp Thr His Pro Gln	
140 145 150	
cgc atg gag aag aaa ctg cat gca gta cct gcg ggg aac acc gtc aag	532
Arg Met Glu Lys Lys Leu His Ala Val Pro Ala Gly Asn Thr Val Lys	
155 160 165	
ttc cgc tgt cca gct gca ggc aac ccc acg ccc acc atc cgc tgg ctt	580
Phe Arg Cys Pro Ala Ala Gly Asn Pro Thr Pro Thr Ile Arg Trp Leu	
170 175 180 185	
aag gat gga cag gcc ttt cat ggg gag aac cgc att gga ggc att cgg	628
Lys Asp Gly Gln Ala Phe His Gly Glu Asn Arg Ile Gly Gly Ile Arg	
190 195 200	
ctg cgc cat cag cac tgg agt ctc gtg atg gag agc gtg gtg ccc tcg	676
Leu Arg His Gln His Trp Ser Leu Val Met Glu Ser Val Val Pro Ser	
205 210 215	
gac cgc ggc aca tac acc tgc ctg gta gag aac gct gtg ggc agc atc	724
Asp Arg Gly Thr Tyr Thr Cys Leu Val Glu Asn Ala Val Gly Ser Ile	
220 225 230	
cgc tat aac tac ctg cta gat gtg ctg gag cgg tcc ccg cac cgg ccc	772
Arg Tyr Asn Tyr Leu Leu Asp Val Leu Glu Arg Ser Pro His Arg Pro	
235 240 245	
atc ctg cag gcc ggg ctc ccg gcc aac acc aca gcc gtg gtg ggc agc	820
Ile Leu Gln Ala Gly Leu Pro Ala Asn Thr Thr Ala Val Val Gly Ser	
250 255 260 265	
gac gtg gag ctg ctg tgc aag gtg tac agc gat gcc cag ccc cac atc	868
Asp Val Glu Leu Leu Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile	
270 275 280	
cag tgg ctg aag cac atc gtc atc aac ggc agc agc ttc gga gcc gac	916
Gln Trp Leu Lys His Ile Val Ile Asn Gly Ser Ser Phe Gly Ala Asp	
285 290 295	

- 58 -

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ggt ttc ccc tat gtg caa gtc cta aag act gca gac atc aat agc tca 964
Gly Phe Pro Tyr Val Gln Val Leu Lys Thr Ala Asp Ile Asn Ser Ser
      300              305              310

gag gtg gag gtc ctg tac ctg cgg aac gtg tca gcc gag gac gca ggc 1012
Glu Val Glu Val Leu Tyr Leu Arg Asn Val Ser Ala Glu Asp Ala Gly
      315              320              325

gag tac acc tgc ctc gca ggc aat tcc atc ggc ctc tcc tac cag tct 1060
Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Leu Ser Tyr Gln Ser
      330              335              340              345

gcc tgg ctc acg gtg ctg cca ggt gag cac ctg aag ggc cag gag atg 1108
Ala Trp Leu Thr Val Leu Pro Gly Glu His Leu Lys Gly Gln Glu Met
      350              355              360

ctg cga gat gcc cct ctg ggc cag cag tgg ggg ctg tgg cct gtt ggg 1156
Leu Arg Asp Ala Pro Leu Gly Gln Gln Trp Gly Leu Trp Pro Val Gly
      365              370              375

tgg tca gtc tct gtt ggc ctg tgg ggt ctg gcc tgg ggg gca gtg tgt 1204
Trp Ser Val Ser Val Gly Leu Trp Gly Leu Ala Trp Gly Ala Val Cys
      380              385              390

gga ttt gtg ggt ttg agc tgt atg aca gcc cct ctg tgc ctc tcc aca 1252
Gly Phe Val Gly Leu Ser Cys Met Thr Ala Pro Leu Cys Leu Ser Thr
      395              400              405

cgt ggc cgt cca tgt gac cgt ctg ctg agg tgt ggg tgc ctg gga ctg 1300
Arg Gly Arg Pro Cys Asp Arg Leu Leu Arg Cys Gly Cys Leu Gly Leu
      410              415              420              425

ggc ata act aca gct tcc tcc gtg tgt gtc ccc aca tat gtt ggg agc 1348
Gly Ile Thr Thr Ala Ser Ser Val Cys Val Pro Thr Tyr Val Gly Ser
      430              435              440

tgg gag gga ctg agt tag ggtgcacggg gcgggccagtc tcaccactga 1396
Trp Glu Gly Leu Ser *
      445

ccagtttgtc tgtctgtgtg tgtccatgtg cgaggggcaga ggaggacccc acatggaccg 1456
cagcagcgcc cgaggccagg tatacggaca tcacccctgta cgcgtcgggc tccctggcct 1516
tggctgtgct cctgctgctg gccgggctgt atcgagggca ggcgctccac ggccggcacc 1576
ccgcccgcgc cgccactgtg cagaagctct cccgcttccc tctggcccga cagttctccc 1636
tggagtcagg ctcttcgggc aagtcaagct catccctggg acgagggcgtg cgtctctcct 1696
ccagcggccc cgccttgctc gccggcctcg tgagtctaga tctacctctc gaccactat 1756
gggagttccc ccgggacag 1775

<210> 121
<211> 446
<212> PRT
<213> Homo Sapiens

<400> 121
Met Arg Leu Leu Leu Ala Leu Leu Gly Val Leu Leu Ser Val Pro Gly
  1              5              10              15

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Pro	Pro	Val	Leu	Ser	Leu	Glu	Ala	Ser	Glu	Glu	Val	Glu	Leu	Glu	Pro
			20					25					30		
Cys	Leu	Ala	Pro	Ser	Leu	Glu	Gln	Gln	Glu	Gln	Glu	Leu	Thr	Val	Ala
		35					40					45			
Leu	Gly	Gln	Pro	Val	Arg	Leu	Cys	Cys	Gly	Arg	Ala	Glu	Arg	Gly	Gly
	50					55					60				
His	Trp	Tyr	Lys	Glu	Gly	Ser	Arg	Leu	Ala	Pro	Ala	Gly	Arg	Val	Arg
65					70						75			80	
Gly	Trp	Arg	Gly	Arg	Leu	Glu	Ile	Ala	Ser	Phe	Leu	Pro	Glu	Asp	Ala
			85						90					95	
Gly	Arg	Tyr	Leu	Cys	Leu	Ala	Arg	Gly	Ser	Met	Ile	Val	Leu	Gln	Asn
			100					105						110	
Leu	Thr	Leu	Ile	Thr	Gly	Asp	Ser	Leu	Thr	Ser	Ser	Asn	Asp	Asp	Glu
	115						120						125		
Asp	Pro	Lys	Ser	His	Arg	Asp	Pro	Ser	Asn	Arg	His	Ser	Tyr	Pro	Gln
	130					135					140				
Gln	Ala	Pro	Tyr	Trp	Thr	His	Pro	Gln	Arg	Met	Glu	Lys	Lys	Leu	His
145					150					155				160	
Ala	Val	Pro	Ala	Gly	Asn	Thr	Val	Lys	Phe	Arg	Cys	Pro	Ala	Ala	Gly
			165						170					175	
Asn	Pro	Thr	Pro	Thr	Ile	Arg	Trp	Leu	Lys	Asp	Gly	Gln	Ala	Phe	His
			180					185						190	
Gly	Glu	Asn	Arg	Ile	Gly	Gly	Ile	Arg	Leu	Arg	His	Gln	His	Trp	Ser
	195						200					205			
Leu	Val	Met	Glu	Ser	Val	Val	Pro	Ser	Asp	Arg	Gly	Thr	Tyr	Thr	Cys
	210					215						220			
Leu	Val	Glu	Asn	Ala	Val	Gly	Ser	Ile	Arg	Tyr	Asn	Tyr	Leu	Leu	Asp
225				230						235				240	
Val	Leu	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile	Leu	Gln	Ala	Gly	Leu	Pro
			245						250					255	
Ala	Asn	Thr	Thr	Ala	Val	Val	Gly	Ser	Asp	Val	Glu	Leu	Leu	Cys	Lys
			260					265					270		
Val	Tyr	Ser	Asp	Ala	Gln	Pro	His	Ile	Gln	Trp	Leu	Lys	His	Ile	Val
	275						280					285			
Ile	Asn	Gly	Ser	Ser	Phe	Gly	Ala	Asp	Gly	Phe	Pro	Tyr	Val	Gln	Val
	290					295					300				
Leu	Lys	Thr	Ala	Asp	Ile	Asn	Ser	Ser	Glu	Val	Glu	Val	Leu	Tyr	Leu
305					310					315				320	
Arg	Asn	Val	Ser	Ala	Glu	Asp	Ala	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly
			325						330				335		
Asn	Ser	Ile	Gly	Leu	Ser	Tyr	Gln	Ser	Ala	Trp	Leu	Thr	Val	Leu	Pro
			340					345					350		
Gly	Glu	His	Leu	Lys	Gly	Gln	Glu	Met	Leu	Arg	Asp	Ala	Pro	Leu	Gly
	355					360						365			
Gln	Gln	Trp	Gly	Leu	Trp	Pro	Val	Gly	Trp	Ser	Val	Ser	Val	Gly	Leu
	370					375					380				
Trp	Gly	Leu	Ala	Trp	Gly	Ala	Val	Cys	Gly	Phe	Val	Gly	Leu	Ser	Cys
385				390						395				400	
Met	Thr	Ala	Pro	Leu	Cys	Leu	Ser	Thr	Arg	Gly	Arg	Pro	Cys	Asp	Arg
			405						410					415	
Leu	Leu	Arg	Cys	Gly	Cys	Leu	Gly	Leu	Gly	Ile	Thr	Thr	Ala	Ser	Ser
			420					425					430		
Val	Cys	Val	Pro	Thr	Tyr	Val	Gly	Ser	Trp	Glu	Gly	Leu	Ser		
		435					440					445			

- 60 -

<210> 122  
 <211> 923  
 <212> DNA  
 <213> Homo Sapiens

<220>  
 <221> CDS  
 <222> (253)...(777)

<400> 122  
 gcggacactc ctctcggctc ctccccggca gcggcgggcg ctcggagcgg gctccggggc 60  
 tcgggtgcag cggccagcgg gcgcctggcg gcgaggatta cccggggaag tggttgtctc 120  
 ctggctggag ccgcgagacg ggcgctcagg gcgcggggcc gccggcggcg aacgagagga 180  
 cggactctgg cggccgggtc gttggccgcg gggagcgcgg gcaccgggcg agcaggccgc 240  
 gtcgcgctca cc atg gtc agc tac tgg gac acc ggg gtc ctg ctg tgc gcg 291  
                   Met Val Ser Tyr Trp Asp Thr Gly Val Leu Leu Cys Ala  
                   1                  5                  10

ctg ctc agc tgt ctg ctt ctc aca gga tct agt tca ggt tca aaa tta 339  
 Leu Leu Ser Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Lys Leu  
                   15                  20                  25

aaa gat cct gaa ctg agt tta aaa ggc acc cag cac atc atg caa gca 387  
 Lys Asp Pro Glu Leu Ser Leu Lys Gly Thr Gln His Ile Met Gln Ala  
                   30                  35                  40                  45

ggc cag aca ctg cat ctc caa tgc agg ggg gaa gca gcc cat aaa tgg 435  
 Gly Gln Thr Leu His Leu Gln Cys Arg Gly Glu Ala Ala His Lys Trp  
                   50                  55                  60

tct ttg cct gaa atg gtg agt aag gaa agc gaa agg ctg agc ata act 483  
 Ser Leu Pro Glu Met Val Ser Lys Glu Ser Glu Arg Leu Ser Ile Thr  
                   65                  70                  75

aaa tct gcc tgt gga aga aat ggc aaa caa ttc tgc agt act tta acc 531  
 Lys Ser Ala Cys Gly Arg Asn Gly Lys Gln Phe Cys Ser Thr Leu Thr  
                   80                  85                  90

ttg aac aca gct caa gca aac cac act ggc ttc tac agc tgc aaa tat 579  
 Leu Asn Thr Ala Gln Ala Asn His Thr Gly Phe Tyr Ser Cys Lys Tyr  
                   95                  100                  105

cta gct gta cct act tca aag aag aag gaa aca gaa tct gca atc tat 627  
 Leu Ala Val Pro Thr Ser Lys Lys Lys Glu Thr Glu Ser Ala Ile Tyr  
                   110                  115                  120                  125

ata ttt att agt gat aca ggt aga cct ttc gta gag atg tac agt gaa 675  
 Ile Phe Ile Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu  
                   130                  135                  140

atc ccc gaa att ata cac atg act gaa gga agg gag ctc gtc att ccc 723  
 Ile Pro Glu Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro  
                   145                  150                  155

tgc cgg gtt acg tca cct aac atc act gtt act tta aaa aag aag aag 771  
 Cys Arg Val Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Lys Lys

- 61 -

160 165 170  
gca taa ggagaaagtc agatcatgga ttattttctt ctgtttggac tcaccgtgct 827  
Ala \*

tgggaatact tctgagcatt agagagcact tcattcattg cagagtctct ggcctccgag 887  
gctgccttca ccatcagcag cttcagcttc tgggag 923

&lt;210&gt; 123

&lt;211&gt; 174

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 123

Met	Val	Ser	Tyr	Trp	Asp	Thr	Gly	Val	Leu	Leu	Cys	Ala	Leu	Leu	Ser
1				5				10					15		
Cys	Leu	Leu	Leu	Thr	Gly	Ser	Ser	Ser	Gly	Ser	Lys	Leu	Lys	Asp	Pro
		20						25				30			
Glu	Leu	Ser	Leu	Lys	Gly	Thr	Gln	His	Ile	Met	Gln	Ala	Gly	Gln	Thr
		35				40					45				
Leu	His	Leu	Gln	Cys	Arg	Gly	Glu	Ala	Ala	His	Lys	Trp	Ser	Leu	Pro
	50					55					60				
Glu	Met	Val	Ser	Lys	Glu	Ser	Glu	Arg	Leu	Ser	Ile	Thr	Lys	Ser	Ala
	65				70					75				80	
Cys	Gly	Arg	Asn	Gly	Lys	Gln	Phe	Cys	Ser	Thr	Leu	Thr	Leu	Asn	Thr
			85					90						95	
Ala	Gln	Ala	Asn	His	Thr	Gly	Phe	Tyr	Ser	Cys	Lys	Tyr	Leu	Ala	Val
		100					105						110		
Pro	Thr	Ser	Lys	Lys	Lys	Glu	Thr	Glu	Ser	Ala	Ile	Tyr	Ile	Phe	Ile
		115					120					125			
Ser	Asp	Thr	Gly	Arg	Pro	Phe	Val	Glu	Met	Tyr	Ser	Glu	Ile	Pro	Glu
	130					135					140				
Ile	Ile	His	Met	Thr	Glu	Gly	Arg	Glu	Leu	Val	Ile	Pro	Cys	Arg	Val
	145				150					155					160
Thr	Ser	Pro	Asn	Ile	Thr	Val	Thr	Leu	Lys	Lys	Lys	Lys	Ala		
			165					170							

&lt;210&gt; 124

&lt;211&gt; 783

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (17)...(700)

&lt;400&gt; 124

cgcgagcgag ccggag atg cag cgg ggc gcc gcg ctg tgc ctg cga ctg tgg 52  
Met Gln Arg Gly Ala Ala Leu Cys Leu Arg Leu Trp  
1 5 10

ctc tgc ctg gga ctc ctg gac ggc ctg gtg agt ggc tac tcc atg acc 100  
Leu Cys Leu Gly Leu Leu Asp Gly Leu Val Ser Gly Tyr Ser Met Thr  
15 20 25

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ccc ccg acc ttg aac atc acg gag gag tca cac gtc atc gac acc ggt 148
Pro Pro Thr Leu Asn Ile Thr Glu Glu Ser His Val Ile Asp Thr Gly
      30              35              40

gac agc ctg tcc atc tcc tgc agg gga cag cac ccc ctc gag tgg gct 196
Asp Ser Leu Ser Ile Ser Cys Arg Gly Gln His Pro Leu Glu Trp Ala
  45              50              55              60

tgg cca gga gct cag gag gcg cca gcc acc gga gac aag gac agc gag 244
Trp Pro Gly Ala Gln Glu Ala Pro Ala Thr Gly Asp Lys Asp Ser Glu
              65              70              75

gac acg ggg gtg gtg cga gac tgc gag ggc aca gac gcc agg ccc tac 292
Asp Thr Gly Val Val Arg Asp Cys Glu Gly Thr Asp Ala Arg Pro Tyr
              80              85              90

tgc aag gtg ttg ctg ctg cac gag gta cat gcc aac gac aca ggc agc 340
Cys Lys Val Leu Leu Leu His Glu Val His Ala Asn Asp Thr Gly Ser
              95              100              105

tac gtc tgc tac tac aag tac atc aag gca cgc atc gag ggc acc acg 388
Tyr Val Cys Tyr Tyr Lys Tyr Ile Lys Ala Arg Ile Glu Gly Thr Thr
  110              115              120

gcc gcc agc tcc tac gtg ttc gtg aga gga agg acg cca tgt ggg tgc 436
Ala Ala Ser Ser Tyr Val Phe Val Arg Gly Arg Thr Pro Cys Gly Cys
  125              130              135              140

cct gtc tgg tgt cca tcc ccg gcc tca atg tca cgc tgc gct cgc aaa 484
Pro Val Trp Cys Pro Ser Pro Ala Ser Met Ser Arg Cys Ala Arg Lys
              145              150              155

gct cgg tgc tgt ggc cag acg ggc agg agg tgg tgt ggg atg acc ggc 532
Ala Arg Cys Cys Gly Gln Thr Gly Arg Arg Trp Cys Gly Met Thr Gly
  160              165              170

ggg gca tgc tcg tgt cca cgc cac tgc tgc acg atg ccc tgt acc tgc 580
Gly Ala Cys Ser Cys Pro Arg His Cys Cys Thr Met Pro Cys Thr Cys
  175              180              185

agt gcg aga cca cct ggg gag acc agg act tcc ttt cca acc cct tcc 628
Ser Ala Arg Pro Pro Gly Glu Thr Arg Thr Ser Phe Pro Thr Pro Ser
  190              195              200

tgg tgc aca tca cag gca acg agc tct atg aca tcc agc tgt tgc cca 676
Trp Cys Thr Ser Gln Ala Thr Ser Ser Met Thr Ser Ser Cys Cys Pro
  205              210              215              220

gga agt cgc tgg agc tgc tgg tag gggagaagct ggtcctgaac tgcaccgtgt 730
Gly Ser Arg Trp Ser Cys Trp *
              225

gggctgagtt taactcaggt gtcacctttg actggggacta cccagggaag cag 783

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<210> 125



- 63 -

<211> 227  
 <212> PRT  
 <213> Homo Sapiens

<400> 125  
 Met Gln Arg Gly Ala Ala Leu Cys Leu Arg Leu Trp Leu Cys Leu Gly  
 1 5 10 15  
 Leu Leu Asp Gly Leu Val Ser Gly Tyr Ser Met Thr Pro Pro Thr Leu  
 20 25 30  
 Asn Ile Thr Glu Glu Ser His Val Ile Asp Thr Gly Asp Ser Leu Ser  
 35 40 45  
 Ile Ser Cys Arg Gly Gln His Pro Leu Glu Trp Ala Trp Pro Gly Ala  
 50 55 60  
 Gln Glu Ala Pro Ala Thr Gly Asp Lys Asp Ser Glu Asp Thr Gly Val  
 65 70 75 80  
 Val Arg Asp Cys Glu Gly Thr Asp Ala Arg Pro Tyr Cys Lys Val Leu  
 85 90 95  
 Leu Leu His Glu Val His Ala Asn Asp Thr Gly Ser Tyr Val Cys Tyr  
 100 105 110  
 Tyr Lys Tyr Ile Lys Ala Arg Ile Glu Gly Thr Thr Ala Ala Ser Ser  
 115 120 125  
 Tyr Val Phe Val Arg Gly Arg Thr Pro Cys Gly Cys Pro Val Trp Cys  
 130 135 140  
 Pro Ser Pro Ala Ser Met Ser Arg Cys Ala Arg Lys Ala Arg Cys Cys  
 145 150 155 160  
 Gly Gln Thr Gly Arg Arg Trp Cys Gly Met Thr Gly Gly Ala Cys Ser  
 165 170 175  
 Cys Pro Arg His Cys Cys Thr Met Pro Cys Thr Cys Ser Ala Arg Pro  
 180 185 190  
 Pro Gly Glu Thr Arg Thr Ser Phe Pro Thr Pro Ser Trp Cys Thr Ser  
 195 200 205  
 Gln Ala Thr Ser Ser Met Thr Ser Ser Cys Cys Pro Gly Ser Arg Trp  
 210 215 220  
 Ser Cys Trp  
 225

<210> 126  
 <211> 1356  
 <212> DNA  
 <213> Homo Sapiens

<220>  
 <221> CDS  
 <222> (16)...(903)

<400> 126  
 gcgcagcggc cggag atg cag cgg ggc gcc gcg ctg tgc ctg cga ctg tgg 51  
 Met Gln Arg Gly Ala Ala Leu Cys Leu Arg Leu Trp  
 1 5 10  
 ctc tgc ctg gga ctc ctg gac ggc ctg gtg agt ggc tac tcc atg acc 99  
 Leu Cys Leu Gly Leu Leu Asp Gly Leu Val Ser Gly Tyr Ser Met Thr  
 15 20 25  
 ccc ccg acc ttg aac atc acg gag gag tca cac gtc atc gac acc ggt 147

- 64 -

Pro	Pro	Thr	Leu	Asn	Ile	Thr	Glu	Glu	Ser	His	Val	Ile	Asp	Thr	Gly	
30						35					40					
gac	agc	ctg	tcc	atc	tcc	tgc	agg	gga	cag	cac	ccc	ctc	gag	tgg	gct	195
Asp	Ser	Leu	Ser	Ile	Ser	Cys	Arg	Gly	Gln	His	Pro	Leu	Glu	Trp	Ala	
45					50					55					60	
tgg	cca	gga	gct	cag	gag	gcg	cca	gcc	acc	gga	gac	aag	gac	agc	gag	243
Trp	Pro	Gly	Ala	Gln	Glu	Ala	Pro	Ala	Thr	Gly	Asp	Lys	Asp	Ser	Glu	
				65					70					75		
gac	acg	ggg	gtg	gtg	cga	gac	tgc	gag	ggc	aca	gac	gcc	agg	ccc	tac	291
Asp	Thr	Gly	Val	Val	Arg	Asp	Cys	Glu	Gly	Thr	Asp	Ala	Arg	Pro	Tyr	
			80					85					90			
tgc	aag	gtg	ttg	ctg	ctg	cac	gag	gta	cat	gcc	aac	gac	aca	ggc	agc	339
Cys	Lys	Val	Leu	Leu	Leu	His	Glu	Val	His	Ala	Asn	Asp	Thr	Gly	Ser	
		95					100					105				
tac	gtc	tgc	tac	tac	aag	tac	atc	aag	gca	cgc	atc	gag	ggc	acc	acg	387
Tyr	Val	Cys	Tyr	Tyr	Lys	Tyr	Ile	Lys	Ala	Arg	Ile	Glu	Gly	Thr	Thr	
	110					115					120					
gcc	gcc	agc	tcc	tac	gtg	ttc	gtg	aga	gac	ttt	gag	cag	cca	ttc	atc	435
Ala	Ala	Ser	Ser	Tyr	Val	Phe	Val	Arg	Asp	Phe	Glu	Gln	Pro	Phe	Ile	
125					130					135					140	
aac	aag	cct	gac	acg	ctc	ttg	gtc	aac	agg	aag	gac	gcc	atg	tgg	gtg	483
Asn	Lys	Pro	Asp	Thr	Leu	Leu	Val	Asn	Arg	Lys	Asp	Ala	Met	Trp	Val	
				145					150					155		
ccc	tgt	ctg	gtg	tcc	atc	ccc	ggc	ctc	aat	gtc	acg	ctg	cgc	tcg	caa	531
Pro	Cys	Leu	Val	Ser	Ile	Pro	Gly	Leu	Asn	Val	Thr	Leu	Arg	Ser	Gln	
			160					165					170			
agc	tcg	gtg	ctg	tgg	cca	gac	ggg	cag	gag	gtg	gtg	tgg	gat	gac	cgg	579
Ser	Ser	Val	Leu	Trp	Pro	Asp	Gly	Gln	Glu	Val	Val	Trp	Asp	Asp	Arg	
		175					180					185				
cgg	ggc	atg	ctc	gtg	tcc	acg	cca	ctg	ctg	cac	gat	gcc	ctg	tac	ctg	627
Arg	Gly	Met	Leu	Val	Ser	Thr	Pro	Leu	Leu	His	Asp	Ala	Leu	Tyr	Leu	
	190					195					200					
cag	tgc	gag	acc	acc	tgg	gga	gac	cag	gac	ttc	ctt	tcc	aac	ccc	ttc	675
Gln	Cys	Glu	Thr	Thr	Trp	Gly	Asp	Gln	Asp	Phe	Leu	Ser	Asn	Pro	Phe	
205					210					215					220	
ctg	gtg	cac	atc	aca	ggc	aac	gag	ctc	tat	gac	atc	cag	ctg	ttg	ccc	723
Leu	Val	His	Ile	Thr	Gly	Asn	Glu	Leu	Tyr	Asp	Ile	Gln	Leu	Leu	Pro	
				225					230					235		
agg	aag	tcg	ctg	gag	ctg	ctg	gta	ggg	gag	aag	ctg	gtc	ctg	aac	tgc	771
Arg	Lys	Ser	Leu	Glu	Leu	Leu	Val	Gly	Glu	Lys	Leu	Val	Leu	Asn	Cys	
			240					245					250			
acc	gtg	tgg	gct	gag	ttt	aac	tca	ggt	gtc	acc	ttt	gac	tgg	gac	tac	819

- 65 -

Thr Val Trp Ala Glu Phe Asn Ser Gly Val Thr Phe Asp Trp Asp Tyr  
 255 260 265

cca ggg aag cag aaa atc cct tca tca gcg tcg agt ggc tca aag gac 867  
 Pro Gly Lys Gln Lys Ile Pro Ser Ser Ala Ser Ser Gly Ser Lys Asp  
 270 275 280

cca tcc tgg agg cca cgg cag gag acg agc tgg tga agctgcccgt 913  
 Pro Ser Trp Arg Pro Arg Gln Glu Thr Ser Trp \*  
 285 290 295

gaagctggca gcgtaccccc cgcccagagt ccagtgggtac aaggatggaa aggcactgtc 973  
 cgggcgcccac agtccacatg ccctgggtgct caaggagggtg acagaggcca gcacaggcac 1033  
 ctacaccctc gccctgtgga actccgctgc tggcctgagg cgcaacatca gcctggagct 1093  
 ggtgggtgaat gtgccccccc agatacatga gaaggaggcc tcctccccca gcatctactc 1153  
 gcgtcacagc cgccaggccc tcacctgcac ggcctacggg gtgcccctgc ctctcagcat 1213  
 ccagtggcac tggcggccct ggacaccctg caagatgttt gccacgcgta gtctccggcg 1273  
 gcggcagcag caagacctca tgccacagtg ccgtgactgg agggcggtga ccacgcagga 1333  
 tgccgtgaac cccatcgaga gcc 1356

<210> 127  
 <211> 295  
 <212> PRT  
 <213> Homo Sapiens

<400> 127  
 Met Gln Arg Gly Ala Ala Leu Cys Leu Arg Leu Trp Leu Cys Leu Gly  
 1 5 10 15  
 Leu Leu Asp Gly Leu Val Ser Gly Tyr Ser Met Thr Pro Pro Thr Leu  
 20 25 30  
 Asn Ile Thr Glu Glu Ser His Val Ile Asp Thr Gly Asp Ser Leu Ser  
 35 40 45  
 Ile Ser Cys Arg Gly Gln His Pro Leu Glu Trp Ala Trp Pro Gly Ala  
 50 55 60  
 Gln Glu Ala Pro Ala Thr Gly Asp Lys Asp Ser Glu Asp Thr Gly Val  
 65 70 75 80  
 Val Arg Asp Cys Glu Gly Thr Asp Ala Arg Pro Tyr Cys Lys Val Leu  
 85 90 95  
 Leu Leu His Glu Val His Ala Asn Asp Thr Gly Ser Tyr Val Cys Tyr  
 100 105 110  
 Tyr Lys Tyr Ile Lys Ala Arg Ile Glu Gly Thr Thr Ala Ala Ser Ser  
 115 120 125  
 Tyr Val Phe Val Arg Asp Phe Glu Gln Pro Phe Ile Asn Lys Pro Asp  
 130 135 140  
 Thr Leu Leu Val Asn Arg Lys Asp Ala Met Trp Val Pro Cys Leu Val  
 145 150 155 160  
 Ser Ile Pro Gly Leu Asn Val Thr Leu Arg Ser Gln Ser Ser Val Leu  
 165 170 175  
 Trp Pro Asp Gly Gln Glu Val Val Trp Asp Asp Arg Arg Gly Met Leu  
 180 185 190  
 Val Ser Thr Pro Leu Leu His Asp Ala Leu Tyr Leu Gln Cys Glu Thr  
 195 200 205  
 Thr Trp Gly Asp Gln Asp Phe Leu Ser Asn Pro Phe Leu Val His Ile  
 210 215 220  
 Thr Gly Asn Glu Leu Tyr Asp Ile Gln Leu Leu Pro Arg Lys Ser Leu  
 225 230 235 240

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Glu Leu Leu Val Gly Glu Lys Leu Val Leu Asn Cys Thr Val Trp Ala  
                           245                          250                          255  
 Glu Phe Asn Ser Gly Val Thr Phe Asp Trp Asp Tyr Pro Gly Lys Gln  
                           260                          265                          270  
 Lys Ile Pro Ser Ser Ala Ser Ser Gly Ser Lys Asp Pro Ser Trp Arg  
                           275                          280                          285  
 Pro Arg Gln Glu Thr Ser Trp  
                           290                          295

<210> 128  
 <211> 1589  
 <212> DNA  
 <213> Homo Sapiens

<220>  
 <221> CDS  
 <222> (29)...(1516)

<400> 128  
 ggatcctcta ggggtcccagc tcgcctcg atg gag ctc ctc ccg ccg ctg cct 52  
   Met Glu Leu Leu Pro Pro Leu Pro  
   1  5

cag tcc ttc ctg ttg ctg ctg ctg ttg cct gcc aag ccc gcg gcg ggc 100  
 Gln Ser Phe Leu Leu Leu Leu Leu Leu Pro Ala Lys Pro Ala Ala Gly  
           10  15  20

gag gac tgg cag tgc ccg cgc acc ccc tac gcg gcc tct cgc gac ttt 148  
 Glu Asp Trp Gln Cys Pro Arg Thr Pro Tyr Ala Ala Ser Arg Asp Phe  
           25  30  35  40

gac gtg aag tac gtg gtg ccc agc ttc tcc gcc gga ggc ctg gta cag 196  
 Asp Val Lys Tyr Val Val Pro Ser Phe Ser Ala Gly Gly Leu Val Gln  
   45  50  55

gcc atg gtg acc tac gag ggc gac aga aat gag agt gct gtg ttt gta 244  
 Ala Met Val Thr Tyr Glu Gly Asp Arg Asn Glu Ser Ala Val Phe Val  
   60  65  70

gcc ata cgc aat cgc ctg cat gtg ctt ggg cct gac ctg aag tct gtc 292  
 Ala Ile Arg Asn Arg Leu His Val Leu Gly Pro Asp Leu Lys Ser Val  
   75  80  85

cag agc ctg gcc acg ggc cct gct gga gac cct ggc tgc cag acg tgt 340  
 Gln Ser Leu Ala Thr Gly Pro Ala Gly Asp Pro Gly Cys Gln Thr Cys  
           90  95  100

gca gcc tgt ggc cca gga ccc cac ggc cct ccc ggt gac aca gac aca 388  
 Ala Ala Cys Gly Pro Gly Pro His Gly Pro Pro Gly Asp Thr Asp Thr  
           105  110  115  120

aag gtg ctg gtg ctg gat ccc gcg ctg cct gcg ctg gtc agt tgt ggc 436  
 Lys Val Leu Val Leu Asp Pro Ala Leu Pro Ala Leu Val Ser Cys Gly  
   125  130  135

- 67 -

tcc agc ctg cag ggc cgc tgc ttc ctg cat gac cta gag ccc caa ggg	484
Ser Ser Leu Gln Gly Arg Cys Phe Leu His Asp Leu Glu Pro Gln Gly	
140 145 150	
aca gcc gtg cat ctg gca gcg cca gcc tgc ctc ttc tca gcc cac cat	532
Thr Ala Val His Leu Ala Ala Pro Ala Cys Leu Phe Ser Ala His His	
155 160 165	
aac cgg ccc gat gac tgc ccc gac tgt gtg gcc agc cca ttg ggc acc	580
Asn Arg Pro Asp Asp Cys Pro Asp Cys Val Ala Ser Pro Leu Gly Thr	
170 175 180	
cgt gta act gtg gtt gag caa ggc cag gcc tcc tat ttc tac gtg gca	628
Arg Val Thr Val Val Glu Gln Gly Gln Ala Ser Tyr Phe Tyr Val Ala	
185 190 195 200	
tcc tca ctg gac gca gcc gtg gct gcc agc ttc agc cca cgc tca gtg	676
Ser Ser Leu Asp Ala Ala Val Ala Ser Phe Ser Pro Arg Ser Val	
205 210 215	
tct atc agg cgt ctc aag gct gac gcc tcg gga ttc gca ccg ggc ttt	724
Ser Ile Arg Arg Leu Lys Ala Asp Ala Ser Gly Phe Ala Pro Gly Phe	
220 225 230	
gtg gcg ttg tca gtg ctg ccc aag cat ctt gtc tcc tac agt att gaa	772
Val Ala Leu Ser Val Leu Pro Lys His Leu Val Ser Tyr Ser Ile Glu	
235 240 245	
tac gtg cac agc ttc cac acg gga gcc ttc gta tac ttc ctg act gta	820
Tyr Val His Ser Phe His Thr Gly Ala Phe Val Tyr Phe Leu Thr Val	
250 255 260	
cag ccg gcc agc gtg aca gat gat cct agt gcc ctg cac aca cgc ctg	868
Gln Pro Ala Ser Val Thr Asp Asp Pro Ser Ala Leu His Thr Arg Leu	
265 270 275 280	
gca cgg ctt agc gcc act gag cca gag ttg ggt gac tat cgg gag ctg	916
Ala Arg Leu Ser Ala Thr Glu Pro Glu Leu Gly Asp Tyr Arg Glu Leu	
285 290 295	
gtc ctc gac tgc aga ttt gct cca aaa cgc agg cgc cgg ggg gcc cca	964
Val Leu Asp Cys Arg Phe Ala Pro Lys Arg Arg Arg Arg Gly Ala Pro	
300 305 310	
gaa ggc gga cag ccc tac cct gtg ctg cgg gtg gcc cac tcc gct cca	1012
Glu Gly Gly Gln Pro Tyr Pro Val Leu Arg Val Ala His Ser Ala Pro	
315 320 325	
gtg ggt gcc caa ctt gcc act gag ctg agc atc gcc gag ggc cag gaa	1060
Val Gly Ala Gln Leu Ala Thr Glu Leu Ser Ile Ala Glu Gly Gln Glu	
330 335 340	
gta cta ttt ggg gtc ttt gtg act ggc aag gat ggt ggt cct ggc gtg	1108
Val Leu Phe Gly Val Phe Val Thr Gly Lys Asp Gly Gly Pro Gly Val	
345 350 355 360	

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ggc ccc aac tct gtc gtc tgt gcc ttc ccc att gac ctg ctg gac aca 1156
Gly Pro Asn Ser Val Val Cys Ala Phe Pro Ile Asp Leu Leu Asp Thr
                365                370                375

cta att gat gag ggt gtg gag cgc tgt tgt gaa tcc cca gtc cat cca 1204
Leu Ile Asp Glu Gly Val Glu Arg Cys Cys Glu Ser Pro Val His Pro
                380                385                390

ggc ctc cgg cga ggc ctc gac ttc ttc cag tcg ccc agt ttt tgc ccc 1252
Gly Leu Arg Arg Gly Leu Asp Phe Phe Gln Ser Pro Ser Phe Cys Pro
                395                400                405

aac ccg cct ggc ctg gaa gcc ctc agc ccc aac acc agc tgc cgc cac 1300
Asn Pro Pro Gly Leu Glu Ala Leu Ser Pro Asn Thr Ser Cys Arg His
                410                415                420

ttc cct ctg ctg gtc agt agc agc ttc tca cgt gtg gac cta ttc aat 1348
Phe Pro Leu Leu Val Ser Ser Ser Phe Ser Arg Val Asp Leu Phe Asn
                425                430                435                440

ggg ctg ttg gga cca gta cag gtc act gca ttg tat gtg aca cgc ctt 1396
Gly Leu Leu Gly Pro Val Gln Val Thr Ala Leu Tyr Val Thr Arg Leu
                445                450                455

gac aac gtc aca gtg gca cac atg ggc aca atg gat ggg cgt atc ctg 1444
Asp Asn Val Thr Val Ala His Met Gly Thr Met Asp Gly Arg Ile Leu
                460                465                470

cag gtg ggt cct cat ccc cac agt ccc cta gcc ctg ggt cct tgt ctc 1492
Gln Val Gly Pro His Pro His Ser Pro Leu Ala Leu Gly Pro Cys Leu
                475                480                485

cat ccc cat ttt gct cac atc tga cctgtcctag gtggagctgg tcaggtcact 1546
His Pro His Phe Ala His Ile *
                490                495

aaactacttg ctgtatgtgt ccaacttctc actgggtgac agt 1589

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&lt;210&gt; 129

&lt;211&gt; 495

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 129

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Met Glu Leu Leu Pro Pro Leu Pro Gln Ser Phe Leu Leu Leu Leu Leu
 1          5          10          15
Leu Pro Ala Lys Pro Ala Ala Gly Glu Asp Trp Gln Cys Pro Arg Thr
 20          25          30
Pro Tyr Ala Ala Ser Arg Asp Phe Asp Val Lys Tyr Val Val Pro Ser
 35          40          45
Phe Ser Ala Gly Gly Leu Val Gln Ala Met Val Thr Tyr Glu Gly Asp
 50          55          60
Arg Asn Glu Ser Ala Val Phe Val Ala Ile Arg Asn Arg Leu His Val
 65          70          75          80
Leu Gly Pro Asp Leu Lys Ser Val Gln Ser Leu Ala Thr Gly Pro Ala
 85          90          95

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Gly	Asp	Pro	Gly	Cys	Gln	Thr	Cys	Ala	Ala	Cys	Gly	Pro	Gly	Pro	His
			100					105					110		
Gly	Pro	Pro	Gly	Asp	Thr	Asp	Thr	Lys	Val	Leu	Val	Leu	Asp	Pro	Ala
			115				120					125			
Leu	Pro	Ala	Leu	Val	Ser	Cys	Gly	Ser	Ser	Leu	Gln	Gly	Arg	Cys	Phe
			130				135				140				
Leu	His	Asp	Leu	Glu	Pro	Gln	Gly	Thr	Ala	Val	His	Leu	Ala	Ala	Pro
145					150					155					160
Ala	Cys	Leu	Phe	Ser	Ala	His	His	Asn	Arg	Pro	Asp	Asp	Cys	Pro	Asp
			165						170					175	
Cys	Val	Ala	Ser	Pro	Leu	Gly	Thr	Arg	Val	Thr	Val	Val	Glu	Gln	Gly
			180					185					190		
Gln	Ala	Ser	Tyr	Phe	Tyr	Val	Ala	Ser	Ser	Leu	Asp	Ala	Ala	Val	Ala
			195				200					205			
Ala	Ser	Phe	Ser	Pro	Arg	Ser	Val	Ser	Ile	Arg	Arg	Leu	Lys	Ala	Asp
			210				215				220				
Ala	Ser	Gly	Phe	Ala	Pro	Gly	Phe	Val	Ala	Leu	Ser	Val	Leu	Pro	Lys
225					230					235					240
His	Leu	Val	Ser	Tyr	Ser	Ile	Glu	Tyr	Val	His	Ser	Phe	His	Thr	Gly
			245						250					255	
Ala	Phe	Val	Tyr	Phe	Leu	Thr	Val	Gln	Pro	Ala	Ser	Val	Thr	Asp	Asp
			260					265					270		
Pro	Ser	Ala	Leu	His	Thr	Arg	Leu	Ala	Arg	Leu	Ser	Ala	Thr	Glu	Pro
			275				280					285			
Glu	Leu	Gly	Asp	Tyr	Arg	Glu	Leu	Val	Leu	Asp	Cys	Arg	Phe	Ala	Pro
			290				295				300				
Lys	Arg	Arg	Arg	Arg	Gly	Ala	Pro	Glu	Gly	Gly	Gln	Pro	Tyr	Pro	Val
305					310					315					320
Leu	Arg	Val	Ala	His	Ser	Ala	Pro	Val	Gly	Ala	Gln	Leu	Ala	Thr	Glu
			325						330					335	
Leu	Ser	Ile	Ala	Glu	Gly	Gln	Glu	Val	Leu	Phe	Gly	Val	Phe	Val	Thr
			340					345					350		
Gly	Lys	Asp	Gly	Gly	Pro	Gly	Val	Gly	Pro	Asn	Ser	Val	Val	Cys	Ala
			355				360					365			
Phe	Pro	Ile	Asp	Leu	Leu	Asp	Thr	Leu	Ile	Asp	Glu	Gly	Val	Glu	Arg
			370				375				380				
Cys	Cys	Glu	Ser	Pro	Val	His	Pro	Gly	Leu	Arg	Arg	Gly	Leu	Asp	Phe
385					390					395					400
Phe	Gln	Ser	Pro	Ser	Phe	Cys	Pro	Asn	Pro	Pro	Gly	Leu	Glu	Ala	Leu
			405						410					415	
Ser	Pro	Asn	Thr	Ser	Cys	Arg	His	Phe	Pro	Leu	Leu	Val	Ser	Ser	Ser
			420					425					430		
Phe	Ser	Arg	Val	Asp	Leu	Phe	Asn	Gly	Leu	Leu	Gly	Pro	Val	Gln	Val
			435				440					445			
Thr	Ala	Leu	Tyr	Val	Thr	Arg	Leu	Asp	Asn	Val	Thr	Val	Ala	His	Met
			450			455					460				
Gly	Thr	Met	Asp	Gly	Arg	Ile	Leu	Gln	Val	Gly	Pro	His	Pro	His	Ser
465					470					475					480
Pro	Leu	Ala	Leu	Gly	Pro	Cys	Leu	His	Pro	His	Phe	Ala	His	Ile	
			485						490					495	

&lt;210&gt; 130

&lt;211&gt; 1505

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (41)...(1144)

&lt;400&gt; 130

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tgcacatttg tggaaactgg atggagagat ttggggaagc atg gac tct tta gcc 55
                                     Met Asp Ser Leu Ala
                                     1           5

agc tta gtt ctc tgt gga gtc agc ttg ctc ctt tct gga act gtg gaa 103
Ser Leu Val Leu Cys Gly Val Ser Leu Leu Leu Ser Gly Thr Val Glu
                        10                        15                        20

ggt gcc atg gac ttg atc ttg atc aat tcc cta cct ctt gta tct gat 151
Gly Ala Met Asp Leu Ile Leu Ile Asn Ser Leu Pro Leu Val Ser Asp
                        25                        30                        35

gct gaa aca tct ctc acc tgc att gcc tct ggg tgg cgc ccc cat gag 199
Ala Glu Thr Ser Leu Thr Cys Ile Ala Ser Gly Trp Arg Pro His Glu
                        40                        45                        50

ccc atc acc ata gga agg gac ttt gaa gcc tta atg aac cag cac cag 247
Pro Ile Thr Ile Gly Arg Asp Phe Glu Ala Leu Met Asn Gln His Gln
                        55                        60                        65

gat ccg ctg gaa gtt act caa gat gtg acc aga gaa tgg gct aaa aaa 295
Asp Pro Leu Glu Val Thr Gln Asp Val Thr Arg Glu Trp Ala Lys Lys
                        70                        75                        80                        85

gtt gtt tgg aag aga gaa aag gct agt aag atc aat ggt gct tat ttc 343
Val Val Trp Lys Arg Glu Lys Ala Ser Lys Ile Asn Gly Ala Tyr Phe
                        90                        95                        100

tgt gaa ggg cga gtt cga gga gag gca atc agg ata cga acc atg aag 391
Cys Glu Gly Arg Val Arg Gly Glu Ala Ile Arg Ile Arg Thr Met Lys
                        105                        110                        115

atg cgt caa caa gct tcc ttc cta cca gct act tta act atg act gtg 439
Met Arg Gln Gln Ala Ser Phe Leu Pro Ala Thr Leu Thr Met Thr Val
                        120                        125                        130

gac aag gga gat aac gtg aac ata tct ttc aaa aag gta ttg att aaa 487
Asp Lys Gly Asp Asn Val Asn Ile Ser Phe Lys Lys Val Leu Ile Lys
                        135                        140                        145

gaa gaa gat gca gtg att tac aaa aat ggt tcc ttc atc cat tca gtg 535
Glu Glu Asp Ala Val Ile Tyr Lys Asn Gly Ser Phe Ile His Ser Val
                        150                        155                        160                        165

ccc cgg cat gaa gta cct gat att cta gaa gta cac ctg cct cat gct 583
Pro Arg His Glu Val Pro Asp Ile Leu Glu Val His Leu Pro His Ala
                        170                        175                        180

cag ccc cag gat gct gga gtg tac tcg gcc agg tat ata gga gga aac 631
Gln Pro Gln Asp Ala Gly Val Tyr Ser Ala Arg Tyr Ile Gly Gly Asn

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185	190	195	
ctc ttc acc tcg gcc ttc acc agg ctg ata gtc cgg aga tgt gaa gcc			679
Leu Phe Thr Ser Ala Phe Thr Arg Leu Ile Val Arg Arg Cys Glu Ala			
200	205	210	
cag aag tgg gga cct gaa tgc aac cat ctc tgt act gct tgt atg aac			727
Gln Lys Trp Gly Pro Glu Cys Asn His Leu Cys Thr Ala Cys Met Asn			
215	220	225	
aat ggt gtc tgc cat gaa gat act gga gaa tgc att tgc cct cct ggg			775
Asn Gly Val Cys His Glu Asp Thr Gly Glu Cys Ile Cys Pro Pro Gly			
230	235	240	245
ttt atg gga agg acg tgt gag aag gct tgt gaa ctg cac acg ttt ggc			823
Phe Met Gly Arg Thr Cys Glu Lys Ala Cys Glu Leu His Thr Phe Gly			
	250	255	260
aga act tgt aaa gaa agg tgc agt gga caa gag gga tgc aag tct tat			871
Arg Thr Cys Lys Glu Arg Cys Ser Gly Gln Glu Gly Cys Lys Ser Tyr			
	265	270	275
gtg ttc tgt ctc cct gac ccc tat ggg tgt tcc tgt gcc aca ggc tgg			919
Val Phe Cys Leu Pro Asp Pro Tyr Gly Cys Ser Cys Ala Thr Gly Trp			
	280	285	290
aag ggt ctg cag tgc aat gaa gca tgc cac cct ggt ttt tac ggg cca			967
Lys Gly Leu Gln Cys Asn Glu Ala Cys His Pro Gly Phe Tyr Gly Pro			
295	300	305	
gat tgt aag ctt agg tgc agc tgc aac aat ggg gag atg tgt gat cgc			1015
Asp Cys Lys Leu Arg Cys Ser Cys Asn Asn Gly Glu Met Cys Asp Arg			
310	315	320	325
ttc caa gga tgt ctc tgc tct cca gga tgg cag ggg ctc cag tgt gag			1063
Phe Gln Gly Cys Leu Cys Ser Pro Gly Trp Gln Gly Leu Gln Cys Glu			
	330	335	340
aga gaa ggt aaa gca agg cat aca gag gat gac ccc aaa gat agt gga			1111
Arg Glu Gly Lys Ala Arg His Thr Glu Asp Asp Pro Lys Asp Ser Gly			
	345	350	355
ttt gcc aga tca tat aga agt aaa cag tgg taa attttaatccc atttgcaaag			1164
Phe Ala Arg Ser Tyr Arg Ser Lys Gln Trp *			
	360	365	
cttctggctg gccgctacct actaatgaag aaatgaccct ggtgaagccg gatgggacag			1224
tgctccatta gccatattca ccatccaccg gatcctcccc cctgactcag gagtttgggt			1284
ctgcagtgtg aacacagtgg ctgggatggg ggaaaagccc ttcaacattt ctgttaaagt			1344
tcttccaaag cccctgaatg ccccaaactg gattgacact ggacataact ttgctgtcat			1404
caacatcagc tctgagcctt actttgggga tggaccaatc aaatccaaga agcttctata			1464
caaacccggt aatcactatg aggcttggca acatattcaa g			1505
<210> 131			
<211> 367			
<212> PRT			

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&lt;213&gt; Homo Sapiens

&lt;400&gt; 131

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Met Asp Ser Leu Ala Ser Leu Val Leu Cys Gly Val Ser Leu Leu Leu
 1          5          10          15
Ser Gly Thr Val Glu Gly Ala Met Asp Leu Ile Leu Ile Asn Ser Leu
 20          25          30
Pro Leu Val Ser Asp Ala Glu Thr Ser Leu Thr Cys Ile Ala Ser Gly
 35          40          45
Trp Arg Pro His Glu Pro Ile Thr Ile Gly Arg Asp Phe Glu Ala Leu
 50          55          60
Met Asn Gln His Gln Asp Pro Leu Glu Val Thr Gln Asp Val Thr Arg
 65          70          75          80
Glu Trp Ala Lys Lys Val Val Trp Lys Arg Glu Lys Ala Ser Lys Ile
 85          90          95
Asn Gly Ala Tyr Phe Cys Glu Gly Arg Val Arg Gly Glu Ala Ile Arg
 100         105         110
Ile Arg Thr Met Lys Met Arg Gln Gln Ala Ser Phe Leu Pro Ala Thr
 115         120         125
Leu Thr Met Thr Val Asp Lys Gly Asp Asn Val Asn Ile Ser Phe Lys
 130         135         140
Lys Val Leu Ile Lys Glu Glu Asp Ala Val Ile Tyr Lys Asn Gly Ser
 145         150         155         160
Phe Ile His Ser Val Pro Arg His Glu Val Pro Asp Ile Leu Glu Val
 165         170         175
His Leu Pro His Ala Gln Pro Gln Asp Ala Gly Val Tyr Ser Ala Arg
 180         185         190
Tyr Ile Gly Gly Asn Leu Phe Thr Ser Ala Phe Thr Arg Leu Ile Val
 195         200         205
Arg Arg Cys Glu Ala Gln Lys Trp Gly Pro Glu Cys Asn His Leu Cys
 210         215         220
Thr Ala Cys Met Asn Asn Gly Val Cys His Glu Asp Thr Gly Glu Cys
 225         230         235         240
Ile Cys Pro Pro Gly Phe Met Gly Arg Thr Cys Glu Lys Ala Cys Glu
 245         250         255
Leu His Thr Phe Gly Arg Thr Cys Lys Glu Arg Cys Ser Gly Gln Glu
 260         265         270
Gly Cys Lys Ser Tyr Val Phe Cys Leu Pro Asp Pro Tyr Gly Cys Ser
 275         280         285
Cys Ala Thr Gly Trp Lys Gly Leu Gln Cys Asn Glu Ala Cys His Pro
 290         295         300
Gly Phe Tyr Gly Pro Asp Cys Lys Leu Arg Cys Ser Cys Asn Asn Gly
 305         310         315         320
Glu Met Cys Asp Arg Phe Gln Gly Cys Leu Cys Ser Pro Gly Trp Gln
 325         330         335
Gly Leu Gln Cys Glu Arg Glu Gly Lys Ala Arg His Thr Glu Asp Asp
 340         345         350
Pro Lys Asp Ser Gly Phe Ala Arg Ser Tyr Arg Ser Lys Gln Trp
 355         360         365

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&lt;210&gt; 132

&lt;211&gt; 1467

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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<222> (41) . . . (1447)
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				Met	Asp	Ser	Leu	Ala								
				1				5								
agc	tta	gtt	ctc	tgt	gga	gtc	agc	ttg	ctc	ctt	tct	gga	act	gtg	gaa	103
Ser	Leu	Val	Leu	Cys	Gly	Val	Ser	Leu	Leu	Leu	Ser	Gly	Thr	Val	Glu	
				10					15					20		
ggt	gcc	atg	gac	ttg	atc	ttg	atc	aat	tcc	cta	cct	ctt	gta	tct	gat	151
Gly	Ala	Met	Asp	Leu	Ile	Leu	Ile	Asn	Ser	Leu	Pro	Leu	Val	Ser	Asp	
			25					30					35			
gct	gaa	aca	tct	ctc	acc	tgc	att	gcc	tct	ggg	tgg	cgc	ccc	cat	gag	199
Ala	Glu	Thr	Ser	Leu	Thr	Cys	Ile	Ala	Ser	Gly	Trp	Arg	Pro	His	Glu	
		40					45					50				
ccc	atc	acc	ata	gga	agg	gac	ttt	gaa	gcc	tta	atg	aac	cag	cac	cag	247
Pro	Ile	Thr	Ile	Gly	Arg	Asp	Phe	Glu	Ala	Leu	Met	Asn	Gln	His	Gln	
	55					60					65					
gat	ccg	ctg	gaa	gtt	act	caa	gat	gtg	acc	aga	gaa	tgg	gct	aaa	aaa	295
Asp	Pro	Leu	Glu	Val	Thr	Gln	Asp	Val	Thr	Arg	Glu	Trp	Ala	Lys	Lys	
					75					80					85	
gtt	gtt	tgg	aag	aga	gaa	aag	gct	agt	aag	atc	aat	ggg	gct	tat	ttc	343
Val	Val	Trp	Lys	Arg	Glu	Lys	Ala	Ser	Lys	Ile	Asn	Gly	Ala	Tyr	Phe	
				90					95					100		
tgt	gaa	ggg	cga	gtt	cga	gga	gag	gca	atc	agg	ata	cga	acc	atg	aag	391
Cys	Glu	Gly	Arg	Val	Arg	Gly	Glu	Ala	Ile	Arg	Ile	Arg	Thr	Met	Lys	
			105					110					115			
atg	cgt	caa	caa	gct	tcc	ttc	cta	cca	gct	act	tta	act	atg	act	gtg	439
Met	Arg	Gln	Gln	Ala	Ser	Phe	Leu	Pro	Ala	Thr	Leu	Thr	Met	Thr	Val	
		120					125					130				
gac	aag	gga	gat	aac	gtg	aac	ata	tct	ttc	aaa	aag	gta	ttg	att	aaa	487
Asp	Lys	Gly	Asp	Asn	Val	Asn	Ile	Ser	Phe	Lys	Lys	Val	Leu	Ile	Lys	
	135					140					145					
gaa	gaa	gat	gca	gtg	att	tac	aaa	aat	ggt	tcc	ttc	atc	cat	tca	gtg	535
Glu	Glu	Asp	Ala	Val	Ile	Tyr	Lys	Asn	Gly	Ser	Phe	Ile	His	Ser	Val	
	150				155					160					165	
ccc	cgg	cat	gaa	gta	cct	gat	att	cta	gaa	gta	cac	ctg	cct	cat	gct	583
Pro	Arg	His	Glu	Val	Pro	Asp	Ile	Leu	Glu	Val	His	Leu	Pro	His	Ala	
				170					175					180		
cag	ccc	cag	gat	gct	gga	gtg	tac	tcg	gcc	agg	tat	ata	gga	gga	aac	631
Gln	Pro	Gln	Asp	Ala	Gly	Val	Tyr	Ser	Ala	Arg	Tyr	Ile	Gly	Gly	Asn	
			185					190					195			

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ctc ttc acc tcg gcc ttc acc agg ctg ata gtc cgg aga tgt gaa gcc	679
Leu Phe Thr Ser Ala Phe Thr Arg Leu Ile Val Arg Arg Cys Glu Ala	
200 205 210	
cag aag tgg gga cct gaa tgc aac cat ctc tgt act gct tgt atg aac	727
Gln Lys Trp Gly Pro Glu Cys Asn His Leu Cys Thr Ala Cys Met Asn	
215 220 225	
aat ggt gtc tgc cat gaa gat act gga gaa tgc att tgc cct cct ggg	775
Asn Gly Val Cys His Glu Asp Thr Gly Glu Cys Ile Cys Pro Pro Gly	
230 235 240 245	
ttt atg gga agg acg tgt gag aag gct tgt gaa ctg cac acg ttt ggc	823
Phe Met Gly Arg Thr Cys Glu Lys Ala Cys Glu Leu His Thr Phe Gly	
250 255 260	
aga act tgt aaa gaa agg tgc agt gga caa gag gga tgc aag tct tat	871
Arg Thr Cys Lys Glu Arg Cys Ser Gly Gln Glu Gly Cys Lys Ser Tyr	
265 270 275	
gtg ttc tgt ctc cct gac ccc tat ggg tgt tcc tgt gcc aca ggc tgg	919
Val Phe Cys Leu Pro Asp Pro Tyr Gly Cys Ser Cys Ala Thr Gly Trp	
280 285 290	
aag ggt ctg cag tgc aat gaa ggc ata cag agg atg acc cca aag ata	967
Lys Gly Leu Gln Cys Asn Glu Gly Ile Gln Arg Met Thr Pro Lys Ile	
295 300 305	
gtg gat ttg cca gat cat ata gaa gta aac agt ggt aaa ttt aat ccc	1015
Val Asp Leu Pro Asp His Ile Glu Val Asn Ser Gly Lys Phe Asn Pro	
310 315 320 325	
att tgc aaa gct tct ggc tgg ccg cta cct act aat gaa gaa atg acc	1063
Ile Cys Lys Ala Ser Gly Trp Pro Leu Pro Thr Asn Glu Glu Met Thr	
330 335 340	
ctg gtg aag ccg gat ggg aca gtg ctc cat cca aaa gac ttt aac cat	1111
Leu Val Lys Pro Asp Gly Thr Val Leu His Pro Lys Asp Phe Asn His	
345 350 355	
acg gat cat ttc tca gta gcc ata ttc acc atc cac cgg atc ctc ccc	1159
Thr Asp His Phe Ser Val Ala Ile Phe Thr Ile His Arg Ile Leu Pro	
360 365 370	
cct gac tca gga gtt tgg gtc tgc agt gtg aac aca gtg gct ggg atg	1207
Pro Asp Ser Gly Val Trp Val Cys Ser Val Asn Thr Val Ala Gly Met	
375 380 385	
gtg gaa aag ccc ttc aac att tct gtt aaa gtt ctt cca aag ccc ctg	1255
Val Glu Lys Pro Phe Asn Ile Ser Val Lys Val Leu Pro Lys Pro Leu	
390 395 400 405	
aat gcc cca aac gtg att gac act gga cat aac ttt gct gtc atc aac	1303
Asn Ala Pro Asn Val Ile Asp Thr Gly His Asn Phe Ala Val Ile Asn	
410 415 420	

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atc agc tct gag cct tac ttt ggg gat gga cca atc aaa tcc aag aag 1351
Ile Ser Ser Glu Pro Tyr Phe Gly Asp Gly Pro Ile Lys Ser Lys Lys
          425          430          435

ctt cta tac aaa ccc gtt aat cac tat gag gct tgg caa cat att caa 1399
Leu Leu Tyr Lys Pro Val Asn His Tyr Glu Ala Trp Gln His Ile Gln
          440          445          450

gta tcc atg gag aaa cag agg ctg act aaa gca aat agt gac aaa tga 1447
Val Ser Met Glu Lys Gln Arg Leu Thr Lys Ala Asn Ser Asp Lys *
          455          460          465

gattggtaca ctcaactatt 1467

<210> 133
<211> 468
<212> PRT
<213> Homo Sapiens

<400> 133
Met Asp Ser Leu Ala Ser Leu Val Leu Cys Gly Val Ser Leu Leu Leu
 1          5          10          15
Ser Gly Thr Val Glu Gly Ala Met Asp Leu Ile Leu Ile Asn Ser Leu
          20          25          30
Pro Leu Val Ser Asp Ala Glu Thr Ser Leu Thr Cys Ile Ala Ser Gly
          35          40          45
Trp Arg Pro His Glu Pro Ile Thr Ile Gly Arg Asp Phe Glu Ala Leu
          50          55          60
Met Asn Gln His Gln Asp Pro Leu Glu Val Thr Gln Asp Val Thr Arg
          65          70          75          80
Glu Trp Ala Lys Lys Val Val Trp Lys Arg Glu Lys Ala Ser Lys Ile
          85          90          95
Asn Gly Ala Tyr Phe Cys Glu Gly Arg Val Arg Gly Glu Ala Ile Arg
          100          105          110
Ile Arg Thr Met Lys Met Arg Gln Gln Ala Ser Phe Leu Pro Ala Thr
          115          120          125
Leu Thr Met Thr Val Asp Lys Gly Asp Asn Val Asn Ile Ser Phe Lys
          130          135          140
Lys Val Leu Ile Lys Glu Glu Asp Ala Val Ile Tyr Lys Asn Gly Ser
          145          150          155          160
Phe Ile His Ser Val Pro Arg His Glu Val Pro Asp Ile Leu Glu Val
          165          170          175
His Leu Pro His Ala Gln Pro Gln Asp Ala Gly Val Tyr Ser Ala Arg
          180          185          190
Tyr Ile Gly Gly Asn Leu Phe Thr Ser Ala Phe Thr Arg Leu Ile Val
          195          200          205
Arg Arg Cys Glu Ala Gln Lys Trp Gly Pro Glu Cys Asn His Leu Cys
          210          215          220
Thr Ala Cys Met Asn Asn Gly Val Cys His Glu Asp Thr Gly Glu Cys
          225          230          235          240
Ile Cys Pro Pro Gly Phe Met Gly Arg Thr Cys Glu Lys Ala Cys Glu
          245          250          255
Leu His Thr Phe Gly Arg Thr Cys Lys Glu Arg Cys Ser Gly Gln Glu
          260          265          270
Gly Cys Lys Ser Tyr Val Phe Cys Leu Pro Asp Pro Tyr Gly Cys Ser

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[illegible]

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<221> CDS
<222> (17) ... (772)
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<400> 134																		
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		1				5					10							
ctc	ttc	ttg	gct	tct	cat	gtg	ggc	gcg	gcg	gtg	gac	ctg	acg	ctg	ctg	100		
Leu	Phe	Leu	Ala	Ser	His	Val	Gly	Ala	Ala	Val	Asp	Leu	Thr	Leu	Leu			
		15					20					25						
gcc	aac	ctg	cgg	ctc	acg	gac	ccc	cag	cgc	ttc	ttc	ctg	act	tgc	gtg	148		
Ala	Asn	Leu	Arg	Leu	Thr	Asp	Pro	Gln	Arg	Phe	Phe	Leu	Thr	Cys	Val			
	30					35					40							
tct	ggg	gag	gcc	ggg	gcg	ggg	agg	ggc	tcg	gac	gcc	tgg	ggc	ccg	ccc	196		
Ser	Gly	Glu	Ala	Gly	Ala	Gly	Arg	Gly	Ser	Asp	Ala	Trp	Gly	Pro	Pro			
45					50					55					60			
ctg	ctg	ctg	gag	aag	gac	gac	cgt	atc	gtg	cgc	acc	ccg	ccc	ggg	cca	244		
Leu	Leu	Leu	Glu	Lys	Asp	Asp	Arg	Ile	Val	Arg	Thr	Pro	Pro	Gly	Pro			
				65					70					75				

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ccc ctg cgc ctg gcg cgc aac ggt tcg cac cag gtc acg ctt cgc ggc 292
Pro Leu Arg Leu Ala Arg Asn Gly Ser His Gln Val Thr Leu Arg Gly
      80                      85                      90

ttc tcc aag ccc tcg gac ctc gtg ggc gtc ttc tcc tgc gtg ggc ggt 340
Phe Ser Lys Pro Ser Asp Leu Val Gly Val Phe Ser Cys Val Gly Gly
      95                      100                      105

gct ggg gcg cgg cgc acg cgc gtc atc tac gtg cac aac agc cct gga 388
Ala Gly Ala Arg Arg Thr Arg Val Ile Tyr Val His Asn Ser Pro Gly
     110                      115                      120

gcc cac ctg ctt cca gac aag gtc aca cac act gtg aac aaa ggt gac 436
Ala His Leu Leu Pro Asp Lys Val Thr His Thr Val Asn Lys Gly Asp
    125                      130                      135                      140

acc gct gta ctt tct gca cgt gtg cac aag gag aag cag aca gac gtg 484
Thr Ala Val Leu Ser Ala Arg Val His Lys Glu Lys Gln Thr Asp Val
      145                      150                      155

atc tgg aag agc aac gga tcc tac ttc tac acc ctg gac tgg cat gaa 532
Ile Trp Lys Ser Asn Gly Ser Tyr Phe Tyr Thr Leu Asp Trp His Glu
      160                      165                      170

gcc cag gat ggg cgg ttc ctg ctg cag ctc cca aat gtg cag cca cca 580
Ala Gln Asp Gly Arg Phe Leu Leu Gln Leu Pro Asn Val Gln Pro Pro
     175                      180                      185

tcg agc ggc atc tac agt gcc act tac ctg gaa gcc agc ccc ctg ggc 628
Ser Ser Gly Ile Tyr Ser Ala Thr Tyr Leu Glu Ala Ser Pro Leu Gly
     190                      195                      200

agc gcc ttc ttt cgg ctc atc gtg cgg ggt cag agg cag agg gca gag 676
Ser Ala Phe Phe Arg Leu Ile Val Arg Gly Gln Arg Gln Arg Ala Glu
    205                      210                      215                      220

gtt gtg ggt agg gtg gga ggc tgg gag ccc tat ggg tac ttc ctg tgg 724
Val Val Gly Arg Val Gly Gly Trp Glu Pro Tyr Gly Tyr Phe Leu Trp
      225                      230                      235

gtc ccc tgg agc ccc tgg atc tcc agt cct cag tgg tca ggt ggg tga 772
Val Pro Trp Ser Pro Trp Ile Ser Ser Pro Gln Trp Ser Gly Gly *
      240                      245                      250

gggtcagctg ctgaagacac cttcctccag gttgtggggc tgggcgctgg gggccaggct 832
gtaccaagga gtgcccagggt tgcctacatg gaggtgtctg ccacgaccat gacggcgaat 892
gtgtatgccc ccctggcttc actggcaccc gctgtgaaca gg 934

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&lt;210&gt; 135

&lt;211&gt; 251

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 135

Met Val Trp Arg Val Pro Pro Phe Leu Leu Pro Ile Leu Phe Leu Ala

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1	5	10	15
Ser His Val Gly Ala Ala Val Asp Leu Thr Leu Leu Ala Asn Leu Arg			
20	25	30	
Leu Thr Asp Pro Gln Arg Phe Phe Leu Thr Cys Val Ser Gly Glu Ala			
35	40	45	
Gly Ala Gly Arg Gly Ser Asp Ala Trp Gly Pro Pro Leu Leu Leu Glu			
50	55	60	
Lys Asp Asp Arg Ile Val Arg Thr Pro Pro Gly Pro Pro Leu Arg Leu			
65	70	75	80
Ala Arg Asn Gly Ser His Gln Val Thr Leu Arg Gly Phe Ser Lys Pro			
85	90	95	
Ser Asp Leu Val Gly Val Phe Ser Cys Val Gly Gly Ala Gly Ala Arg			
100	105	110	
Arg Thr Arg Val Ile Tyr Val His Asn Ser Pro Gly Ala His Leu Leu			
115	120	125	
Pro Asp Lys Val Thr His Thr Val Asn Lys Gly Asp Thr Ala Val Leu			
130	135	140	
Ser Ala Arg Val His Lys Glu Lys Gln Thr Asp Val Ile Trp Lys Ser			
145	150	155	160
Asn Gly Ser Tyr Phe Tyr Thr Leu Asp Trp His Glu Ala Gln Asp Gly			
165	170	175	
Arg Phe Leu Leu Gln Leu Pro Asn Val Gln Pro Pro Ser Ser Gly Ile			
180	185	190	
Tyr Ser Ala Thr Tyr Leu Glu Ala Ser Pro Leu Gly Ser Ala Phe Phe			
195	200	205	
Arg Leu Ile Val Arg Gly Gln Arg Gln Arg Ala Glu Val Val Gly Arg			
210	215	220	
Val Gly Gly Trp Glu Pro Tyr Gly Tyr Phe Leu Trp Val Pro Trp Ser			
225	230	235	240
Pro Trp Ile Ser Ser Pro Gln Trp Ser Gly Gly			
245	250		

<210> 136  
 <211> 1619  
 <212> DNA  
 <213> Homo Sapiens

<220>  
 <221> CDS  
 <222> (14)...(1153)

<400> 136	
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Met Val Trp Arg Val Pro Pro Phe Leu Leu Pro Ile	
1 5 10	
ctc ttc ttg gct tct cat gtg ggc gcg gcg gtg gac ctg acg ctg ctg	97
Leu Phe Leu Ala Ser His Val Gly Ala Ala Val Asp Leu Thr Leu Leu	
15 20 25	
gcc aac ctg cgg ctc acg gac ccc cag cgc ttc ttc ctg act tgc gtg	145
Ala Asn Leu Arg Leu Thr Asp Pro Gln Arg Phe Phe Leu Thr Cys Val	
30 35 40	
tct ggg gag gcc ggg gcg ggg agg ggc tcg gac gcc tgg ggc ccg ccc	193



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Ser 45	Gly	Glu	Ala	Gly	Ala	Gly	Arg	Gly	Ser	Asp 55	Ala	Trp	Gly	Pro	Pro 60	
ctg	ctg	ctg	gag	aag	gac	gac	cgt	atc	gtg	cgc	acc	ccg	ccc	ggg	cca	241
Leu	Leu	Leu	Glu	Lys 65	Asp	Asp	Arg	Ile	Val 70	Arg	Thr	Pro	Pro	Gly 75	Pro	
ccc	ctg	cgc	ctg	gcg	cgc	aac	ggt	tcg	cac	cag	gtc	acg	ctt	cgc	ggc	289
Pro	Leu	Arg	Leu	Ala 80	Arg	Asn	Gly	Ser 85	His	Gln	Val	Thr	Leu	Arg	Gly 90	
ttc	tcc	aag	ccc	tcg	gac	ctc	gtg	ggc	gtc	ttc	tcc	tgc	gtg	ggc	ggg	337
Phe	Ser	Lys 95	Pro	Ser	Asp	Leu	Val 100	Gly	Val	Phe	Ser	Cys	Val	Gly	Gly	
gct	ggg	gcg	cgg	cgc	acg	cgc	gtc	atc	tac	gtg	cac	aac	agc	cct	gga	385
Ala	Gly	Ala	Arg	Arg	Thr	Val	Ile 115	Tyr	Val	His	Asn	Ser	Pro	Gly		
gcc	cac	ctg	ctt	cca	gac	aag	gtc	aca	cac	act	gtg	aac	aaa	ggg	gac	433
Ala	His	Leu	Leu	Pro	Asp 130	Lys	Val	Thr	His	Thr 135	Val	Asn	Lys	Gly	Asp 140	
acc	gct	gta	ctt	tct	gca	cgt	gtg	cac	aag	gag	aag	cag	aca	gac	gtg	481
Thr	Ala	Val	Leu	Ser	Ala 145	Arg	Val	His	Lys 150	Glu	Lys	Gln	Thr	Asp	Val 155	
atc	tgg	aag	agc	aac	gga	tcc	tac	ttc	tac	acc	ctg	gac	tgg	cat	gaa	529
Ile	Trp	Lys 160	Ser	Asn	Gly	Ser	Tyr 165	Phe	Tyr	Thr	Leu	Asp	Trp 170	His	Glu	
gcc	cag	gat	ggg	cgg	ttc	ctg	ctg	cag	ctc	cca	aat	gtg	cag	cca	cca	577
Ala	Gln	Asp 175	Gly	Arg	Phe	Leu	Leu 180	Gln	Leu	Pro	Asn	Val 185	Gln	Pro	Pro	
tcg	agc	ggc	atc	tac	agt	gcc	act	tac	ctg	gaa	gcc	agc	ccc	ctg	ggc	625
Ser	Ser	Gly 190	Ile	Tyr	Ser	Ala 195	Thr	Tyr	Leu	Glu	Ala 200	Ser	Pro	Leu	Gly	
agc	gcc	ttc	ttt	cgg	ctc	atc	gtg	cgg	ggg	tgt	ggg	gct	ggg	cgc	tgg	673
Ser	Ala	Phe	Phe	Arg	Leu 210	Ile	Val	Arg	Gly	Cys 215	Gly	Ala	Gly	Arg	Trp 220	
ggg	cca	ggc	tgt	acc	aag	gag	tgc	cca	ggg	tgc	cta	cat	gga	ggg	gtc	721
Gly	Pro	Gly	Cys	Thr 225	Lys	Glu	Cys	Pro	Gly 230	Cys	Leu	His	Gly	Gly	Val 235	
tgc	cac	gac	cat	gac	ggc	gaa	tgt	gta	tgc	ccc	cct	ggc	ttc	act	ggc	769
Cys	His	Asp 240	His	Asp	Gly	Glu	Cys 245	Val	Cys	Pro	Pro	Gly	Phe	Thr	Gly 250	
acc	cgc	tgt	gaa	cag	gcc	tgc	aga	gag	ggc	cgt	ttt	ggg	cag	agc	tgc	817
Thr	Arg	Cys 255	Glu	Gln	Ala	Cys	Arg 260	Glu	Gly	Arg	Phe	Gly 265	Gln	Ser	Cys	
cag	gag	cag	tgc	cca	ggc	ata	tca	ggc	tgc	cgg	ggc	ctc	acc	ttc	tgc	865

- 80 -

Gln Glu Gln Cys Pro Gly Ile Ser Gly Cys Arg Gly Leu Thr Phe Cys  
 270 275 280

ctc cca gac ccc tat ggc tgc tct tgt gga tct ggc tgg aga gga agc 913  
 Leu Pro Asp Pro Tyr Gly Cys Ser Cys Gly Ser Gly Trp Arg Gly Ser  
 285 290 295 300

cag tgc caa gaa gct tgt gcc cct ggt cat ttt ggg gct gat tgc cga 961  
 Gln Cys Gln Glu Ala Cys Ala Pro Gly His Phe Gly Ala Asp Cys Arg  
 305 310 315

ctc cag tgc cag tgt cag aat ggt ggc act tgt gac cgg ttc agt ggt 1009  
 Leu Gln Cys Gln Cys Gln Asn Gly Gly Thr Cys Asp Arg Phe Ser Gly  
 320 325 330

tgt gtc tgc ccc tct ggg tgg cat gga gtg cac tgt gag aag tca ggc 1057  
 Cys Val Cys Pro Ser Gly Trp His Gly Val His Cys Glu Lys Ser Gly  
 335 340 345

tgg agg gac tgg gta gat acc tcc act gag aaa cag aac acg gat gag 1105  
 Trp Arg Asp Trp Val Asp Thr Ser Thr Glu Lys Gln Asn Thr Asp Glu  
 350 355 360

ggg cgc ttt ggt ggt cac gtg tct gcc cct gtg gga gct cca gga tga 1153  
 Gly Arg Phe Gly Gly His Val Ser Ala Pro Val Gly Ala Pro Gly \*  
 365 370 375

gtgtcctttc tccccagacc ggatccccca gatcctcaac atggcctcag aactggagtt 1213  
 caacttagag acgatgcccc ggatcaactg tgcagctgca ggggaaccct tccccgtgcg 1273  
 gggcagcata gagctacgca agccagacgg cactgtgctc ctgtccacca aggccattgt 1333  
 ggagccagag aagaccacag ctgagttcga ggtgccccgc ttggttcttg cggacagtgg 1393  
 gttctggggag tgccgtgtgt ccacatctgg cggccaagac agccggcgct tcaagggtcaa 1453  
 tgtgaaagtg cccccgtgc ccttggtgc acctcggtc ctgaccaagc agagccgcca 1513  
 gcttggtggtc tccccgtgg tctcgttctc tggggatgga cccatctcca ctgtccgcct 1573  
 gcactaccgg ccccaggaca gtaccatgga ctggtcgacc attgtg 1619

<210> 137  
 <211> 379  
 <212> PRT  
 <213> Homo Sapiens

<400> 137  
 Met Val Trp Arg Val Pro Pro Phe Leu Leu Pro Ile Leu Phe Leu Ala  
 1 5 10 15  
 Ser His Val Gly Ala Ala Val Asp Leu Thr Leu Leu Ala Asn Leu Arg  
 20 25 30  
 Leu Thr Asp Pro Gln Arg Phe Phe Leu Thr Cys Val Ser Gly Glu Ala  
 35 40 45  
 Gly Ala Gly Arg Gly Ser Asp Ala Trp Gly Pro Pro Leu Leu Leu Glu  
 50 55 60  
 Lys Asp Asp Arg Ile Val Arg Thr Pro Pro Gly Pro Pro Leu Arg Leu  
 65 70 75 80  
 Ala Arg Asn Gly Ser His Gln Val Thr Leu Arg Gly Phe Ser Lys Pro  
 85 90 95  
 Ser Asp Leu Val Gly Val Phe Ser Cys Val Gly Gly Ala Gly Ala Arg  
 100 105 110

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Arg Thr Arg Val Ile Tyr Val His Asn Ser Pro Gly Ala His Leu Leu
      115      120      125
Pro Asp Lys Val Thr His Thr Val Asn Lys Gly Asp Thr Ala Val Leu
      130      135      140
Ser Ala Arg Val His Lys Glu Lys Gln Thr Asp Val Ile Trp Lys Ser
      145      150      155      160
Asn Gly Ser Tyr Phe Tyr Thr Leu Asp Trp His Glu Ala Gln Asp Gly
      165      170      175
Arg Phe Leu Leu Gln Leu Pro Asn Val Gln Pro Pro Ser Ser Gly Ile
      180      185      190
Tyr Ser Ala Thr Tyr Leu Glu Ala Ser Pro Leu Gly Ser Ala Phe Phe
      195      200      205
Arg Leu Ile Val Arg Gly Cys Gly Ala Gly Arg Trp Gly Pro Gly Cys
      210      215      220
Thr Lys Glu Cys Pro Gly Cys Leu His Gly Gly Val Cys His Asp His
      225      230      235      240
Asp Gly Glu Cys Val Cys Pro Pro Gly Phe Thr Gly Thr Arg Cys Glu
      245      250      255
Gln Ala Cys Arg Glu Gly Arg Phe Gly Gln Ser Cys Gln Glu Gln Cys
      260      265      270
Pro Gly Ile Ser Gly Cys Arg Gly Leu Thr Phe Cys Leu Pro Asp Pro
      275      280      285
Tyr Gly Cys Ser Cys Gly Ser Gly Trp Arg Gly Ser Gln Cys Gln Glu
      290      295      300
Ala Cys Ala Pro Gly His Phe Gly Ala Asp Cys Arg Leu Gln Cys Gln
      305      310      315      320
Cys Gln Asn Gly Gly Thr Cys Asp Arg Phe Ser Gly Cys Val Cys Pro
      325      330      335
Ser Gly Trp His Gly Val His Cys Glu Lys Ser Gly Trp Arg Asp Trp
      340      345      350
Val Asp Thr Ser Thr Glu Lys Gln Asn Thr Asp Glu Gly Arg Phe Gly
      355      360      365
Gly His Val Ser Ala Pro Val Gly Ala Pro Gly
      370      375

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<210> 138  
 <211> 740  
 <212> DNA  
 <213> Homo Sapiens

<220>  
 <221> CDS  
 <222> (34)...(519)

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<400> 138
tcgtcctggc tggcctgggt cggcctctgg agt atg gtc tgg cgg gtg ccc cct 54
      Met Val Trp Arg Val Pro Pro
      1      5

ttc ttg ctc ccc atc ctc ttc ttg gct tct cat gtg ggc gcg gcg gtg 102
Phe Leu Leu Pro Ile Leu Phe Leu Ala Ser His Val Gly Ala Ala Val
      10      15      20

gac ctg acg ctg ctg gcc aac ctg cgg ctc acg gac ccc cag cgc ttc 150
Asp Leu Thr Leu Leu Ala Asn Leu Arg Leu Thr Asp Pro Gln Arg Phe

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25	30	35	
ttc ctg act tgc gtg tct ggg gag gcc ggg gcg ggg agg ggc tcg gac			198
Phe Leu Thr Cys Val Ser Gly Glu Ala Gly Ala Gly Arg Gly Ser Asp			
40	45	50	55
gcc tgg ggc ccg ccc ctg ctg ctg gag aag gac gac cgt atc gtg cgc			246
Ala Trp Gly Pro Pro Leu Leu Leu Glu Lys Asp Asp Arg Ile Val Arg			
	60	65	70
acc ccg ccc ggg cca ccc ctg cgc ctg gcg cgc aac ggt tcg cac cag			294
Thr Pro Pro Gly Pro Pro Leu Arg Leu Ala Arg Asn Gly Ser His Gln			
	75	80	85
gtc acg ctt cgc ggc ttc tcc aag ccc tcg gac ctc gtg ggc gtc ttc			342
Val Thr Leu Arg Gly Phe Ser Lys Pro Ser Asp Leu Val Gly Val Phe			
	90	95	100
tcc tgc gtg ggc ggt gct ggg gcg cgg cgc acg cgc gtc atc tac gtg			390
Ser Cys Val Gly Gly Ala Gly Ala Arg Arg Thr Arg Val Ile Tyr Val			
	105	110	115
cac aac agc cct gga ggt gag tta ggc agg cgg ggg gat ggc gcg ggg			438
His Asn Ser Pro Gly Gly Glu Leu Gly Arg Arg Gly Asp Gly Ala Gly			
	120	125	130
aaa acc agg ccg ctg acc cac ctt cca ccc cgc agc cca cct gct tcc			486
Lys Thr Arg Pro Leu Thr His Leu Pro Pro Arg Ser Pro Pro Ala Ser			
	140	145	150
aga caa ggt cac aca cac tgt gaa caa agg tga caccgctgta ctttctgcac			539
Arg Gln Gly His Thr His Cys Glu Gln Arg *			
	155	160	
gtgtgcacaa ggagaagcag acagacgtga tctggaagag caacggatcc tacttctaca			599
ccctggactg gcatgaagcc caggatgggc gggtcctgct gcagctccca aatgtgcagc			659
caccatcgag cggcatctac agtgccactt acctggaagc cagccccctg ggcagcgcct			719
tctttcggct catcgtgcgg g			740
<210> 139			
<211> 161			
<212> PRT			
<213> Homo Sapiens			
<400> 139			
Met Val Trp Arg Val Pro Pro Phe Leu Leu Pro Ile Leu Phe Leu Ala			
1	5	10	15
Ser His Val Gly Ala Ala Val Asp Leu Thr Leu Leu Ala Asn Leu Arg			
	20	25	30
Leu Thr Asp Pro Gln Arg Phe Phe Leu Thr Cys Val Ser Gly Glu Ala			
	35	40	45
Gly Ala Gly Arg Gly Ser Asp Ala Trp Gly Pro Pro Leu Leu Leu Glu			
	50	55	60
Lys Asp Asp Arg Ile Val Arg Thr Pro Pro Gly Pro Pro Leu Arg Leu			
	65	70	75
Ala Arg Asn Gly Ser His Gln Val Thr Leu Arg Gly Phe Ser Lys Pro			80

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[illegible]

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<210> 140
<211> 1761
<212> DNA
<213> Homo Sapiens
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<220>
<221> CDS
<222> (14)...(1258)
```

[illegible]

- 84 -

Ala	His	Leu	Leu	Pro	Asp	Lys	Val	Thr	His	Thr	Val	Asn	Lys	Gly	Asp	
125					130					135					140	
acc	gct	gta	ctt	tct	gca	cgt	gtg	cac	aag	gag	aag	cag	aca	gac	gtg	481
Thr	Ala	Val	Leu	Ser	Ala	Arg	Val	His	Lys	Glu	Lys	Gln	Thr	Asp	Val	
				145					150					155		
atc	tgg	aag	agc	aac	gga	tcc	tac	ttc	tac	acc	ctg	gac	tgg	cat	gaa	529
Ile	Trp	Lys	Ser	Asn	Gly	Ser	Tyr	Phe	Tyr	Thr	Leu	Asp	Trp	His	Glu	
			160					165					170			
gcc	cag	gat	ggg	cgg	ttc	ctg	ctg	cag	ctc	cca	aat	gtg	cag	cca	cca	577
Ala	Gln	Asp	Gly	Arg	Phe	Leu	Leu	Gln	Leu	Pro	Asn	Val	Gln	Pro	Pro	
		175					180					185				
tcg	agc	ggc	atc	tac	agt	gcc	act	tac	ctg	gaa	gcc	agc	ccc	ctg	ggc	625
Ser	Ser	Gly	Ile	Tyr	Ser	Ala	Thr	Tyr	Leu	Glu	Ala	Ser	Pro	Leu	Gly	
	190					195					200					
agc	gcc	ttc	ttt	cgg	ctc	atc	gtg	cgg	ggg	tgt	ggg	gct	ggg	cgc	tgg	673
Ser	Ala	Phe	Phe	Arg	Leu	Ile	Val	Arg	Gly	Cys	Gly	Ala	Gly	Arg	Trp	
205					210					215					220	
ggg	cca	ggc	tgt	acc	aag	gag	tgc	cca	ggg	tgc	cta	cat	gga	ggg	gtc	721
Gly	Pro	Gly	Cys	Thr	Lys	Glu	Cys	Pro	Gly	Cys	Leu	His	Gly	Gly	Val	
				225					230					235		
tgc	cac	gac	cat	gac	ggc	gaa	tgt	gta	tgc	ccc	cct	ggc	ttc	act	ggc	769
Cys	His	Asp	His	Asp	Gly	Glu	Cys	Val	Cys	Pro	Pro	Gly	Phe	Thr	Gly	
			240					245					250			
acc	cgc	tgt	gaa	cag	gcc	tgc	aga	gag	ggc	cgt	ttt	ggg	cag	agc	tgc	817
Thr	Arg	Cys	Glu	Gln	Ala	Cys	Arg	Glu	Gly	Arg	Phe	Gly	Gln	Ser	Cys	
		255					260					265				
cag	gag	cag	tgc	cca	ggc	ata	tca	ggc	tgc	cgg	ggc	ctc	acc	ttc	tgc	865
Gln	Glu	Gln	Cys	Pro	Gly	Ile	Ser	Gly	Cys	Arg	Gly	Leu	Thr	Phe	Cys	
	270					275					280					
ctc	cca	gac	ccc	tat	ggc	tgc	tct	tgt	gga	tct	ggc	tgg	aga	gga	agc	913
Leu	Pro	Asp	Pro	Tyr	Gly	Cys	Ser	Cys	Gly	Ser	Gly	Trp	Arg	Gly	Ser	
285					290					295					300	
cag	tgc	caa	gaa	gct	tgt	gcc	cct	ggg	cat	ttt	ggg	gct	gat	tgc	cga	961
Gln	Cys	Gln	Glu	Ala	Cys	Ala	Pro	Gly	His	Phe	Gly	Ala	Asp	Cys	Arg	
				305					310					315		
ctc	cag	tgc	cag	tgt	cag	aat	ggg	ggc	act	tgt	gac	cgg	ttc	agt	ggg	1009
Leu	Gln	Cys	Gln	Cys	Gln	Asn	Gly	Gly	Thr	Cys	Asp	Arg	Phe	Ser	Gly	
			320					325					330			
tgt	gtc	tgc	ccc	tct	ggg	tgg	cat	gga	gtg	cac	tgt	gag	aag	tca	gac	1057
Cys	Val	Cys	Pro	Ser	Gly	Trp	His	Gly	Val	His	Cys	Glu	Lys	Ser	Asp	
		335					340					345				
cgg	atc	ccc	cag	atc	ctc	aac	atg	gcc	tca	gaa	ctg	gag	ttc	aac	tta	1105

Arg 350	Ile	Pro	Gln	Ile	Leu	Asn	Met	Ala	Ser	Glu	Leu	Glu	Phe	Asn	Leu	
gag Glu 365	acg Thr	atg Met	ccc Pro	cgg Arg	atc Ile 370	aac Asn	tgt Cys	gca Ala	gct Ala	gca Ala 375	ggg Gly	aac Asn	ccc Pro	ttc Phe	ccc Pro 380	1153
gtg Val	cgg Arg	ggc Gly	agc Ser	ata Ile 385	gag Glu	cta Leu	cgc Arg	aag Lys	cca Pro 390	gac Asp	ggc Gly	act Thr	gtg Val	ctc Leu 395	ctg Leu	1201
gtc Val	agc Ser	ccc Pro	caa Gln 400	tca Ser	ccc Pro	caa Gln	ccc Pro	acc Thr 405	agc Ser	ccc Pro	tca Ser	ggc Gly	cgc Arg 410	ctg Leu	ctt Leu	1249
cac His	agc Ser	tga *	tccctaagac			ccctagatcc			ctcagaactt			tctgcagggc				1298

caaccatttg	gcctgaccat	tgctcacatg	aggtcaggct	gattgggtgag	ggggctgcca	1358
ctgggcctct	gtcctgccat	cagtcacagac	ggacaccttg	gtgcctgcca	cagagggtgc	1418
cgttccctgt	gacatgtccc	cttcccccat	ctctttttagt	ccaccaggcc	cattgtggag	1478
ccagagaaga	ccacagctga	gtctcgagggtg	ccccgcttgg	ttcttcggga	cagtggggttc	1538
tgggagtgcc	gtgtgtccac	atctggcggc	caagacagcc	ggcgcttcaa	gggtcaatgtg	1598
aaagtgcgcc	ccgtgcccc	ggctgcacgt	cggctcctga	ccaagcagag	ccgccagctt	1658
gtgggtctcc	cgctggcttc	gttctctcgg	gattggaccga	ttctccactgt	ccgcctgcac	1718
taccggcccc	aggcagctac	catggactgg	tcgaccattg	tgg		1761

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<210> 141
<211> 414
<212> PRT
<213> Homo Sapiens
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<400> 141																
Met	Val	Trp	Arg	Val	Pro	Pro	Phe	Leu	Leu	Pro	Ile	Leu	Phe	Leu	Ala	
1				5					10					15		
Ser	His	Val	Gly	Ala	Ala	Val	Asp	Leu	Thr	Leu	Leu	Ala	Asn	Leu	Arg	
			20					25					30			
Leu	Thr	Asp	Pro	Gln	Arg	Phe	Phe	Leu	Thr	Cys	Val	Ser	Gly	Glu	Ala	
		35					40					45				
Gly	Ala	Gly	Arg	Gly	Ser	Asp	Ala	Trp	Gly	Pro	Pro	Pro	Leu	Leu	Leu	Glu
		50				55					60					
Lys	Asp	Asp	Arg	Ile	Val	Arg	Thr	Pro	Pro	Gly	Pro	Pro	Leu	Arg	Leu	
65					70					75					80	
Ala	Arg	Asn	Gly	Ser	His	Gln	Val	Thr	Leu	Arg	Gly	Phe	Ser	Lys	Pro	
				85					90					95		
Ser	Asp	Leu	Val	Gly	Val	Phe	Ser	Cys	Val	Gly	Gly	Ala	Gly	Ala	Arg	
			100					105					110			
Arg	Thr	Arg	Val	Ile	Tyr	Val	His	Asn	Ser	Pro	Gly	Ala	His	Leu	Leu	
		115					120					125				
Pro	Asp	Lys	Val	Thr	His	Thr	Val	Asn	Lys	Gly	Asp	Thr	Ala	Val	Leu	
		130				135					140					
Ser	Ala	Arg	Val	His	Lys	Glu	Lys	Gln	Thr	Asp	Val	Ile	Trp	Lys	Ser	
145					150					155					160	
Asn	Gly	Ser	Tyr	Phe	Tyr	Thr	Leu	Asp	Trp	His	Glu	Ala	Gln	Asp	Gly	
				165					170					175		

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Arg Phe Leu Leu Gln Leu Pro Asn Val Gln Pro Pro Ser Ser Gly Ile  
                   180                  185                  190  
 Tyr Ser Ala Thr Tyr Leu Glu Ala Ser Pro Leu Gly Ser Ala Phe Phe  
                   195                  200                  205  
 Arg Leu Ile Val Arg Gly Cys Gly Ala Gly Arg Trp Gly Pro Gly Cys  
                   210                  215                  220  
 Thr Lys Glu Cys Pro Gly Cys Leu His Gly Gly Val Cys His Asp His  
                   225                  230                  235                  240  
 Asp Gly Glu Cys Val Cys Pro Pro Gly Phe Thr Gly Thr Arg Cys Glu  
                   245                  250                  255  
 Gln Ala Cys Arg Glu Gly Arg Phe Gly Gln Ser Cys Gln Glu Gln Cys  
                   260                  265                  270  
 Pro Gly Ile Ser Gly Cys Arg Gly Leu Thr Phe Cys Leu Pro Asp Pro  
                   275                  280                  285  
 Tyr Gly Cys Ser Cys Gly Ser Gly Trp Arg Gly Ser Gln Cys Gln Glu  
                   290                  295                  300  
 Ala Cys Ala Pro Gly His Phe Gly Ala Asp Cys Arg Leu Gln Cys Gln  
                   305                  310                  315                  320  
 Cys Gln Asn Gly Gly Thr Cys Asp Arg Phe Ser Gly Cys Val Cys Pro  
                   325                  330                  335  
 Ser Gly Trp His Gly Val His Cys Glu Lys Ser Asp Arg Ile Pro Gln  
                   340                  345                  350  
 Ile Leu Asn Met Ala Ser Glu Leu Glu Phe Asn Leu Glu Thr Met Pro  
                   355                  360                  365  
 Arg Ile Asn Cys Ala Ala Gly Asn Pro Phe Pro Val Arg Gly Ser  
                   370                  375                  380  
 Ile Glu Leu Arg Lys Pro Asp Gly Thr Val Leu Leu Val Ser Pro Gln  
                   385                  390                  395                  400  
 Ser Pro Gln Pro Thr Ser Pro Ser Gly Arg Leu Leu His Ser  
                   405                  410

&lt;210&gt; 142

&lt;211&gt; 1230

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (14)...(967)

&lt;400&gt; 142

cggcctctctgg agt atg gtc tgg cgg gtg ccc cct ttc ttg ctc ccc atc 49  
                   Met Val Trp Arg Val Pro Pro Phe Leu Leu Pro Ile  
                   1                  5                  10

ctc ttc ttg gct tct cat gtg ggc gcg gcg gtg gac ctg acg ctg ctg 97  
 Leu Phe Leu Ala Ser His Val Gly Ala Ala Val Asp Leu Thr Leu Leu  
                   15                  20                  25

gcc aac ctg cgg ctc acg gac ccc cag cgc ttc ttc ctg act tgc gtg 145  
 Ala Asn Leu Arg Leu Thr Asp Pro Gln Arg Phe Phe Leu Thr Cys Val  
                   30                  35                  40

tct ggg gag gcc ggg gcg ggg agg ggc tcg gac gcc tgg ggc ccg ccc 193  
 Ser Gly Glu Ala Gly Ala Gly Arg Gly Ser Asp Ala Trp Gly Pro Pro



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45	50	55	60	
ctg ctg ctg gag aag gac gac cgt atc gtg cgc acc ccg ccc ggg cca	Leu Leu Leu Glu Lys Asp Asp Arg Ile Val Arg Thr Pro Pro Gly Pro	241		
	65	70	75	
ccc ctg cgc ctg gcg cgc aac ggt tcg cac cag gtc acg ctt cgc ggc	Pro Leu Arg Leu Ala Arg Asn Gly Ser His Gln Val Thr Leu Arg Gly	289		
	80	85	90	
ttc tcc aag ccc tcg gac ctc gtg ggc gtc ttc tcc tgc gtg ggc ggt	Phe Ser Lys Pro Ser Asp Leu Val Gly Val Phe Ser Cys Val Gly Gly	337		
	95	100	105	
gct ggg gcg cgg cgc acg cgc gtc atc tac gtg cac aac agc cct gga	Ala Gly Ala Arg Arg Thr Arg Val Ile Tyr Val His Asn Ser Pro Gly	385		
	110	115	120	
gcc cac ctg ctt cca gac aag gtc aca cac act gtg aac aaa ggt gac	Ala His Leu Leu Pro Asp Lys Val Thr His Thr Val Asn Lys Gly Asp	433		
	125	130	135	140
acc gct gta ctt tct gca cgt gtg cac aag gag aag cag aca gac gtg	Thr Ala Val Leu Ser Ala Arg Val His Lys Glu Lys Gln Thr Asp Val	481		
	145	150	155	
atc tgg aag agc aac gga tcc tac ttc tac acc ctg gac tgg cat gaa	Ile Trp Lys Ser Asn Gly Ser Tyr Phe Tyr Thr Leu Asp Trp His Glu	529		
	160	165	170	
gcc cag gat ggg cgg ttc ctg ctg cag ctc cca aat gtg cag cca cca	Ala Gln Asp Gly Arg Phe Leu Leu Gln Leu Pro Asn Val Gln Pro Pro	577		
	175	180	185	
tcg agc ggc atc tac agt gcc act tac ctg gaa gcc agc ccc ctg ggc	Ser Ser Gly Ile Tyr Ser Ala Thr Tyr Leu Glu Ala Ser Pro Leu Gly	625		
	190	195	200	
agc gcc ttc ttt cgg ctc atc gtg cgg ggt tgt ggg gct ggg cgc tgg	Ser Ala Phe Phe Arg Leu Ile Val Arg Gly Cys Gly Ala Gly Arg Trp	673		
	205	210	215	220
ggg cca ggc tgt acc aag gag tgc cca ggt tgc cta cat gga ggt gtc	Gly Pro Gly Cys Thr Lys Glu Cys Pro Gly Cys Leu His Gly Gly Val	721		
	225	230	235	
tgc cac gac cat gac ggc gaa tgt gta tgc ccc cct ggc ttc act ggc	Cys His Asp His Asp Gly Glu Cys Val Cys Pro Pro Gly Phe Thr Gly	769		
	240	245	250	
acc cgc tgt gaa cag gcc tgc aga gag ggc cgt ttt ggg cag agc tgc	Thr Arg Cys Glu Gln Ala Cys Arg Glu Gly Arg Phe Gly Gln Ser Cys	817		
	255	260	265	
cag gag cag tgc cca ggc ata tca ggc tgc cgg ggc ctc acc ttc tgc	Gln Glu Gln Cys Pro Gly Ile Ser Gly Cys Arg Gly Leu Thr Phe Cys	865		

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270          275          280
ctc cca gac ccc tat ggc tgc tct tgt gga tct ggc tgg aga gga agc 913
Leu Pro Asp Pro Tyr Gly Cys Ser Cys Gly Ser Gly Trp Arg Gly Ser
285          290          295          300
cag tgc caa gaa gtc cac caa ggc cat tgt gga gcc aga gaa gac cac 961
Gln Cys Gln Glu Val His Gln Gly His Cys Gly Ala Arg Glu Asp His
305          310          315
agc tga gttcgaggtg ccccgcttgg ttcttgcgga cagtgggttc tgggagtgcc 1017
Ser *

gtgtgtccac atctggcggc caagacagcc ggcgcttcaa ggtcaatgtg aaagtgcccc 1077
ccgtgccccct ggctgcacct cggctcctga ccaagcagag ccgccagctt gtgggtctccc 1137
cgctgggtctc gttctctggg gatggaccca tctccactgt ccgcctgcac taccggcccc 1197
aggacagtac catggactgg tcgaccattg tgg          1230

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<210> 143  
 <211> 317  
 <212> PRT  
 <213> Homo Sapiens

```

<400> 143
Met Val Trp Arg Val Pro Pro Phe Leu Leu Pro Ile Leu Phe Leu Ala
1          5          10          15
Ser His Val Gly Ala Ala Val Asp Leu Thr Leu Leu Ala Asn Leu Arg
20          25          30
Leu Thr Asp Pro Gln Arg Phe Phe Leu Thr Cys Val Ser Gly Glu Ala
35          40          45
Gly Ala Gly Arg Gly Ser Asp Ala Trp Gly Pro Pro Leu Leu Leu Glu
50          55          60
Lys Asp Asp Arg Ile Val Arg Thr Pro Pro Gly Pro Pro Leu Arg Leu
65          70          75          80
Ala Arg Asn Gly Ser His Gln Val Thr Leu Arg Gly Phe Ser Lys Pro
85          90          95
Ser Asp Leu Val Gly Val Phe Ser Cys Val Gly Gly Ala Gly Ala Arg
100          105          110
Arg Thr Arg Val Ile Tyr Val His Asn Ser Pro Gly Ala His Leu Leu
115          120          125
Pro Asp Lys Val Thr His Thr Val Asn Lys Gly Asp Thr Ala Val Leu
130          135          140
Ser Ala Arg Val His Lys Glu Lys Gln Thr Asp Val Ile Trp Lys Ser
145          150          155          160
Asn Gly Ser Tyr Phe Tyr Thr Leu Asp Trp His Glu Ala Gln Asp Gly
165          170          175
Arg Phe Leu Leu Gln Leu Pro Asn Val Gln Pro Pro Ser Ser Gly Ile
180          185          190
Tyr Ser Ala Thr Tyr Leu Glu Ala Ser Pro Leu Gly Ser Ala Phe Phe
195          200          205
Arg Leu Ile Val Arg Gly Cys Gly Ala Gly Arg Trp Gly Pro Gly Cys
210          215          220
Thr Lys Glu Cys Pro Gly Cys Leu His Gly Gly Val Cys His Asp His
225          230          235          240
Asp Gly Glu Cys Val Cys Pro Pro Gly Phe Thr Gly Thr Arg Cys Glu

```

				245				250				255			
Gln	Ala	Cys	Arg	Glu	Gly	Arg	Phe	Gly	Gln	Ser	Cys	Gln	Glu	Gln	Cys
				260				265				270			
Pro	Gly	Ile	Ser	Gly	Cys	Arg	Gly	Leu	Thr	Phe	Cys	Leu	Pro	Asp	Pro
				275				280				285			
Tyr	Gly	Cys	Ser	Cys	Gly	Ser	Gly	Trp	Arg	Gly	Ser	Gln	Cys	Gln	Glu
				290				295				300			
Val	His	Gln	Gly	His	Cys	Gly	Ala	Arg	Glu	Asp	His	Ser			
				305				310				315			

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<220>
<221> CDS
<222> (24) ... (944)
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<400> 144																	
cctgccactt	ccccaccgag	gcc	atg	ggc	cca	gga	gtt	ctg	ctg	ctc	ctg	ctg	53				
			Met	Gly	Pro	Gly	Val	Leu	Leu	Leu	Leu	Leu					
			1				5					10					
gtg	gcc	aca	gct	tgg	cat	ggg	cag	gga	atc	cca	gtg	ata	gag	ccc	agt	101	
Val	Ala	Thr	Ala	Trp	His	Gly	Gln	Gly	Ile	Pro	Val	Ile	Glu	Pro	Ser		
			15						20					25			
gtc	cct	gag	ctg	gtc	gtg	aag	cca	gga	gca	acg	gtg	acc	ttg	cga	tgt	149	
Val	Pro	Glu	Leu	Val	Val	Lys	Pro	Gly	Ala	Thr	Val	Thr	Leu	Arg	Cys		
			30					35					40				
gtg	ggc	aat	ggc	agc	gtg	gaa	tgg	gat	ggc	ccc	cca	tca	cct	cac	tgg	197	
Val	Gly	Asn	Gly	Ser	Val	Glu	Trp	Asp	Gly	Pro	Pro	Ser	Pro	His	Trp		
		45					50					55					
acc	ctg	tac	tct	gat	ggc	tcc	agc	agc	atc	ctc	agc	acc	aac	aac	gct	245	
Thr	Leu	Tyr	Ser	Asp	Gly	Ser	Ser	Ser	Ile	Leu	Ser	Thr	Asn	Asn	Ala		
	60					65					70						
acc	ttc	caa	aac	acg	ggg	acc	tat	cgc	tgc	act	gag	cct	gga	gac	ccc	293	
Thr	Phe	Gln	Asn	Thr	Gly	Thr	Tyr	Arg	Cys	Thr	Glu	Pro	Gly	Asp	Pro		
	75				80					85					90		
ctg	gga	ggc	agc	gcc	gcc	atc	cac	ctc	tat	gtc	aaa	gac	cct	gcc	cgg	341	
Leu	Gly	Gly	Ser	Ala	Ala	Ile	His	Leu	Tyr	Val	Lys	Asp	Pro	Ala	Arg		
				95					100					105			
ccc	tgg	aac	gtg	cta	gca	cag	gag	gtg	gtc	gtg	ttc	gag	gac	cag	gac	389	
Pro	Trp	Asn	Val	Leu	Ala	Gln	Glu	Val	Val	Val	Phe	Glu	Asp	Gln	Asp		
			110					115					120				
gca	cta	ctg	ccc	tgt	ctg	ctc	aca	gac	ccg	gtg	ctg	gaa	gca	ggc	gtc	437	
Ala	Leu	Leu	Pro	Cys	Leu	Leu	Thr	Asp	Pro	Val	Leu	Glu	Ala	Gly	Val		
		125					130					135					

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tcg ctg gtg cgt gtg cgt ggc cgg ccc ctc atg cgc cac acc aac tac 485
Ser Leu Val Arg Val Arg Gly Arg Pro Leu Met Arg His Thr Asn Tyr
140 145 150

tcc ttc tcg ccc tgg cat ggc ttc acc atc cac agg gcc aag ttc att 533
Ser Phe Ser Pro Trp His Gly Phe Thr Ile His Arg Ala Lys Phe Ile
155 160 165 170

cag agc cag gac tat caa tgc agt gcc ctg atg ggt ggc agg aag gtg 581
Gln Ser Gln Asp Tyr Gln Cys Ser Ala Leu Met Gly Gly Arg Lys Val
175 180 185

atg tcc atc agc atc cgg ctg aaa gtg cag aaa gtc atc cca ggg ccc 629
Met Ser Ile Ser Ile Arg Leu Lys Val Gln Lys Val Ile Pro Gly Pro
190 195 200

cca gcc ttg aca ctg gtg cct gca gag ctg gtg cgg att cga ggg gag 677
Pro Ala Leu Thr Leu Val Pro Ala Glu Leu Val Arg Ile Arg Gly Glu
205 210 215

gct gcc cag atc gtg tgc tca gcc agc agc gtt gat gtt aac ttt gat 725
Ala Ala Gln Ile Val Cys Ser Ala Ser Ser Val Asp Val Asn Phe Asp
220 225 230

gtc ttc ctc caa cac aac aac acc aag ctc gca atc cct caa caa tct 773
Val Phe Leu Gln His Asn Asn Thr Lys Leu Ala Ile Pro Gln Gln Ser
235 240 245 250

gac ttt cat aat aac cgt tac caa aaa gtc ctg acc ctc aac ctc gat 821
Asp Phe His Asn Asn Arg Tyr Gln Lys Val Leu Thr Leu Asn Leu Asp
255 260 265

caa gta gat ttc caa cat gcc ggc aac tac tcc tgc gtg gcc agc aac 869
Gln Val Asp Phe Gln His Ala Gly Asn Tyr Ser Cys Val Ala Ser Asn
270 275 280

gtg cag ggc aag cac tcc acc tcc atg ttc ttc cgg gtg gta ggc aca 917
Val Gln Gly Lys His Ser Thr Met Phe Phe Arg Val Val Gly Thr
285 290 295

cct tca ccc tct ctc tgc ccc gcc tga agccctctga ggctggccgc 964
Pro Ser Pro Ser Leu Cys Pro Ala *
300 305

tactccttcc tggccagaaa ccaggaggc tggagagctc tgacgtttga gctcaccctt 1024
cgataccccc cagaggtaag cgtcatatgg acattcatca acggctctgg cacccttttg 1084
tgtgctgcct ctgggtaccc ccagcccaac gtgacatggc tgcagtgcag tggccacact 1144
gatagggtgtg atgaggccca agtgctgcag gtctgggatg acccataccc tgaggtcctg 1204
agccaggagc ccttccacaa ggtgacgggtg cagagcctgc tgactgttga gaccttagag 1264
cacaacaaaa cctacgagtg cagggccccc aacagcgtgg ggagtggctc ctgggccttc 1324
ataccca 1331

<210> 145
<211> 306
<212> PRT

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&lt;213&gt; Homo Sapiens

&lt;400&gt; 145

```

Met Gly Pro Gly Val Leu Leu Leu Leu Leu Val Ala Thr Ala Trp His
 1           5           10           15
Gly Gln Gly Ile Pro Val Ile Glu Pro Ser Val Pro Glu Leu Val Val
 20           25           30
Lys Pro Gly Ala Thr Val Thr Leu Arg Cys Val Gly Asn Gly Ser Val
 35           40           45
Glu Trp Asp Gly Pro Pro Ser Pro His Trp Thr Leu Tyr Ser Asp Gly
 50           55           60
Ser Ser Ser Ile Leu Ser Thr Asn Asn Ala Thr Phe Gln Asn Thr Gly
 65           70           75           80
Thr Tyr Arg Cys Thr Glu Pro Gly Asp Pro Leu Gly Gly Ser Ala Ala
 85           90           95
Ile His Leu Tyr Val Lys Asp Pro Ala Arg Pro Trp Asn Val Leu Ala
 100          105          110
Gln Glu Val Val Val Phe Glu Asp Gln Asp Ala Leu Leu Pro Cys Leu
 115          120          125
Leu Thr Asp Pro Val Leu Glu Ala Gly Val Ser Leu Val Arg Val Arg
 130          135          140
Gly Arg Pro Leu Met Arg His Thr Asn Tyr Ser Phe Ser Pro Trp His
 145          150          155          160
Gly Phe Thr Ile His Arg Ala Lys Phe Ile Gln Ser Gln Asp Tyr Gln
 165          170          175
Cys Ser Ala Leu Met Gly Gly Arg Lys Val Met Ser Ile Ser Ile Arg
 180          185          190
Leu Lys Val Gln Lys Val Ile Pro Gly Pro Pro Ala Leu Thr Leu Val
 195          200          205
Pro Ala Glu Leu Val Arg Ile Arg Gly Glu Ala Ala Gln Ile Val Cys
 210          215          220
Ser Ala Ser Ser Val Asp Val Asn Phe Asp Val Phe Leu Gln His Asn
 225          230          235          240
Asn Thr Lys Leu Ala Ile Pro Gln Gln Ser Asp Phe His Asn Asn Arg
 245          250          255
Tyr Gln Lys Val Leu Thr Leu Asn Leu Asp Gln Val Asp Phe Gln His
 260          265          270
Ala Gly Asn Tyr Ser Cys Val Ala Ser Asn Val Gln Gly Lys His Ser
 275          280          285
Thr Ser Met Phe Phe Arg Val Val Gly Thr Pro Ser Pro Ser Leu Cys
 290          295          300
Pro Ala
305

```

&lt;210&gt; 146

&lt;211&gt; 1508

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (7)...(1017)

&lt;400&gt; 146

gacacc atg cgg ctt ccg ggt gcg atg cca gct ctg gcc ctc aaa ggc

48

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Met	Arg	Leu	Pro	Gly	Ala	Met	Pro	Ala	Leu	Ala	Leu	Lys	Gly			
1				5					10							
gag	ctg	ctg	ttg	ctg	tct	ctc	ctg	tta	ctt	ctg	gaa	cca	cag	atc	tct	96
Glu	Leu	Leu	Leu	Leu	Ser	Leu	Leu	Leu	Leu	Leu	Glu	Pro	Gln	Ile	Ser	
15					20					25					30	
cag	ggc	ctg	gtc	gtc	aca	ccc	ccg	ggg	cca	gag	ctt	gtc	ctc	aat	gtc	144
Gln	Gly	Leu	Val	Val	Thr	Pro	Pro	Gly	Pro	Glu	Leu	Val	Leu	Asn	Val	
			35					40						45		
tcc	agc	acc	ttc	gtt	ctg	acc	tgc	tgc	ggg	tca	gct	ccg	gtg	gtg	tgg	192
Ser	Ser	Thr	Phe	Val	Leu	Thr	Cys	Ser	Gly	Ser	Ala	Pro	Val	Val	Trp	
			50					55						60		
gaa	cgg	atg	tcc	cag	gag	ccc	cca	cag	gaa	atg	gcc	aag	gcc	cag	gat	240
Glu	Arg	Met	Ser	Gln	Glu	Pro	Pro	Gln	Glu	Met	Ala	Lys	Ala	Gln	Asp	
		65					70					75				
ggc	acc	ttc	tcc	agc	gtg	ctc	aca	ctg	acc	aac	ctc	act	ggg	cta	gac	288
Gly	Thr	Phe	Ser	Ser	Val	Leu	Thr	Leu	Thr	Asn	Leu	Thr	Gly	Leu	Asp	
	80					85					90					
acg	gga	gaa	tac	ttt	tgc	acc	cac	aat	gac	tcc	cgt	gga	ctg	gag	acc	336
Thr	Gly	Glu	Tyr	Phe	Cys	Thr	His	Asn	Asp	Ser	Arg	Gly	Leu	Glu	Thr	
95					100					105					110	
gat	gag	cgg	aaa	cgg	ctc	tac	atc	ttt	gtg	cca	gat	ccc	acc	gtg	ggc	384
Asp	Glu	Arg	Lys	Arg	Leu	Tyr	Ile	Phe	Val	Pro	Asp	Pro	Thr	Val	Gly	
				115					120					125		
ttc	ctc	cct	aat	gat	gcc	gag	gaa	cta	ttc	atc	ttt	ctc	acg	gaa	ata	432
Phe	Leu	Pro	Asn	Asp	Ala	Glu	Glu	Leu	Phe	Ile	Phe	Leu	Thr	Glu	Ile	
			130					135						140		
act	gag	atc	acc	att	cca	tgc	cga	gta	aca	gac	cca	cag	ctg	gtg	gtg	480
Thr	Glu	Ile	Thr	Ile	Pro	Cys	Arg	Val	Thr	Asp	Pro	Gln	Leu	Val	Val	
		145					150					155				
aca	ctg	cac	gag	aag	aaa	ggg	gac	gtt	gca	ctg	cct	gtc	ccc	tat	gat	528
Thr	Leu	His	Glu	Lys	Lys	Gly	Asp	Val	Ala	Leu	Pro	Val	Pro	Tyr	Asp	
	160					165					170					
cac	caa	cgt	ggc	ttt	tct	ggg	atc	ttt	gag	gac	aga	agc	tac	atc	tgc	576
His	Gln	Arg	Gly	Phe	Ser	Gly	Ile	Phe	Glu	Asp	Arg	Ser	Tyr	Ile	Cys	
175					180					185					190	
aaa	acc	acc	att	ggg	gac	agg	gag	gtg	gat	tct	gat	gcc	tac	tat	gtc	624
Lys	Thr	Thr	Ile	Gly	Asp	Arg	Glu	Val	Asp	Ser	Asp	Ala	Tyr	Tyr	Val	
				195					200					205		
tac	aga	ctc	cag	gtg	tca	tcc	atc	aac	gtc	tct	gtg	aac	gca	gtg	cag	672
Tyr	Arg	Leu	Gln	Val	Ser	Ser	Ile	Asn	Val	Ser	Val	Asn	Ala	Val	Gln	
			210					215					220			
act	gtg	gtc	cgc	cag	ggg	gag	aac	atc	acc	ctc	atg	tgc	att	gtg	atc	720

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Thr Val Val Arg Gln Gly Glu Asn Ile Thr Leu Met Cys Ile Val Ile
      225                      230                      235

ggg aat gag gtg gtc aac ttc gag tgg aca tac ccc cgc aaa gaa agt 768
Gly Asn Glu Val Val Asn Phe Glu Trp Thr Tyr Pro Arg Lys Glu Ser
      240                      245                      250

ggg cgg ctg gtg gag ccg gtg act gac ttc ctc ttg gat atg cct tac 816
Gly Arg Leu Val Glu Pro Val Thr Asp Phe Leu Leu Asp Met Pro Tyr
      255                      260                      265                      270

cac atc cgc tcc atc ctg cac atc ccc agt gcc gag tta gaa gac tcg 864
His Ile Arg Ser Ile Leu His Ile Pro Ser Ala Glu Leu Glu Asp Ser
      275                      280                      285

ggg acc tac acc tgc aat gtg acg gag agt gtg aat gac cat cag gat 912
Gly Thr Tyr Thr Cys Asn Val Thr Glu Ser Val Asn Asp His Gln Asp
      290                      295                      300

gaa aag gcc atc aac atc acc gtg aga gcg gct acg tgc ggc tcc tgg 960
Glu Lys Ala Ile Asn Ile Thr Val Arg Ala Ala Thr Cys Gly Ser Trp
      305                      310                      315

gag agg tgg gca cac tac aat ttg ctg agc tgc atc gga gcc gga cac 1008
Glu Arg Trp Ala His Tyr Asn Leu Leu Ser Cys Ile Gly Ala Gly His
      320                      325                      330

tgc agg tag tgttcgaggc ctaccaccgc cccactgtcc tgtgggttcaa 1057
Cys Arg *
      335

agacaaccgc accctgggcg actccagcgc tggcgaaatc gccctgtcca cgcgcaacgt 1117
gtcggagacc cggtatgtgt cagagctgac actgggttcgc gtgaagggtgg cagaggctgg 1177
ccactacacc atgcgggcct tccatgagga tgctgagggtc cagctctcct tccagctaca 1237
gatcaatgtc cctgtccgag tgctggagct aagtgagagc caccctgaca gtggggaaca 1297
gacagtccgc tgtcgtggcc ggggcatgcc ccagccgaac atcatctggt ctgcctgcag 1357
agacctcaaa aggtgtccac gtgagctgcc gccacgctg ctggggaaca gttccgaaga 1417
ggagagccag ctggagacta acgtgacgta ctgggaggag gagcaggagt ttgagggtgg 1477
gagcacactg cgtctgcagc acgtggatcg g 1508

<210> 147
<211> 336
<212> PRT
<213> Homo Sapiens

<400> 147
Met Arg Leu Pro Gly Ala Met Pro Ala Leu Ala Leu Lys Gly Glu Leu
  1      5      10      15
Leu Leu Leu Ser Leu Leu Leu Leu Leu Glu Pro Gln Ile Ser Gln Gly
      20      25      30
Leu Val Val Thr Pro Pro Gly Pro Glu Leu Val Leu Asn Val Ser Ser
      35      40      45
Thr Phe Val Leu Thr Cys Ser Gly Ser Ala Pro Val Val Trp Glu Arg
      50      55      60
Met Ser Gln Glu Pro Pro Gln Glu Met Ala Lys Ala Gln Asp Gly Thr
      65      70      75      80

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Phe Ser Ser Val Leu Thr Leu Thr Asn Leu Thr Gly Leu Asp Thr Gly
      85      90      95
Glu Tyr Phe Cys Thr His Asn Asp Ser Arg Gly Leu Glu Thr Asp Glu
      100      105      110
Arg Lys Arg Leu Tyr Ile Phe Val Pro Asp Pro Thr Val Gly Phe Leu
      115      120      125
Pro Asn Asp Ala Glu Glu Leu Phe Ile Phe Leu Thr Glu Ile Thr Glu
      130      135      140
Ile Thr Ile Pro Cys Arg Val Thr Asp Pro Gln Leu Val Val Thr Leu
      145      150      155      160
His Glu Lys Lys Gly Asp Val Ala Leu Pro Val Pro Tyr Asp His Gln
      165      170      175
Arg Gly Phe Ser Gly Ile Phe Glu Asp Arg Ser Tyr Ile Cys Lys Thr
      180      185      190
Thr Ile Gly Asp Arg Glu Val Asp Ser Asp Ala Tyr Tyr Val Tyr Arg
      195      200      205
Leu Gln Val Ser Ser Ile Asn Val Ser Val Asn Ala Val Gln Thr Val
      210      215      220
Val Arg Gln Gly Glu Asn Ile Thr Leu Met Cys Ile Val Ile Gly Asn
      225      230      235      240
Glu Val Val Asn Phe Glu Trp Thr Tyr Pro Arg Lys Glu Ser Gly Arg
      245      250      255
Leu Val Glu Pro Val Thr Asp Phe Leu Leu Asp Met Pro Tyr His Ile
      260      265      270
Arg Ser Ile Leu His Ile Pro Ser Ala Glu Leu Glu Asp Ser Gly Thr
      275      280      285
Tyr Thr Cys Asn Val Thr Glu Ser Val Asn Asp His Gln Asp Glu Lys
      290      295      300
Ala Ile Asn Ile Thr Val Arg Ala Ala Thr Cys Gly Ser Trp Glu Arg
      305      310      315      320
Trp Ala His Tyr Asn Leu Leu Ser Cys Ile Gly Ala Gly His Cys Arg
      325      330      335

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<210> 148  
 <211> 1683  
 <212> DNA  
 <213> Homo Sapiens

<220>  
 <221> CDS  
 <222> (20) ... (1444)

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<400> 148
cagggtcccgg cccggagct atg gag cgg cgc tgg ccc ctg ggg cta ggg ctg 52
      Met Glu Arg Arg Trp Pro Leu Gly Leu Gly Leu
      1      5      10

gtg ctg ctg ctc tgc gcc ccg ctg ccc ccg ggg gcg cgc gcc aag gaa 100
Val Leu Leu Leu Cys Ala Pro Leu Pro Pro Gly Ala Arg Ala Lys Glu
      15      20      25

gtt act ctg atg gac aca agc aag gca cag gga gag ctg ggc tgg ctg 148
Val Thr Leu Met Asp Thr Ser Lys Ala Gln Gly Glu Leu Gly Trp Leu
      30      35      40

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ctg gat ccc cca aaa gat ggg tgg agt gaa cag caa cag ata ctg aat	196
Leu Asp Pro Pro Lys Asp Gly Trp Ser Glu Gln Gln Gln Ile Leu Asn	
45 50 55	
ggg aca ccc ctg tac atg tac cag gac tgc cca atg caa gga cgc aga	244
Gly Thr Pro Leu Tyr Met Tyr Gln Asp Cys Pro Met Gln Gly Arg Arg	
60 65 70 75	
gac act gac cac tgg ctt cgc tcc aat tgg atc tac cgc ggg gag gag	292
Asp Thr Asp His Trp Leu Arg Ser Asn Trp Ile Tyr Arg Gly Glu Glu	
80 85 90	
gct tcc cgc gtc cac gtg gag ctg cag ttc acc gtg cgg gac tgc aag	340
Ala Ser Arg Val His Val Glu Leu Gln Phe Thr Val Arg Asp Cys Lys	
95 100 105	
agt ttc cct ggg gga gcc ggg cct ctg ggc tgc aag gag acc ttc aac	388
Ser Phe Pro Gly Gly Ala Gly Pro Leu Gly Cys Lys Glu Thr Phe Asn	
110 115 120	
ctt ctg tac atg gag agt gac cag gat gtg ggc att cag ctc cga cgg	436
Leu Leu Tyr Met Glu Ser Asp Gln Asp Val Gly Ile Gln Leu Arg Arg	
125 130 135	
ccc ttg ttc cag aag gta acc acg gtg gct gca gac cag agc ttc acc	484
Pro Leu Phe Gln Lys Val Thr Thr Val Ala Ala Asp Gln Ser Phe Thr	
140 145 150 155	
att cga gac ctt gtg tct ggc tcc gtg aag ctg aat gtg gag cgc tgc	532
Ile Arg Asp Leu Val Ser Gly Ser Val Lys Leu Asn Val Glu Arg Cys	
160 165 170	
tct ctg ggc cgc ctg acc cgc cgt ggc ctc tac ctc gct ttc cac aac	580
Ser Leu Gly Arg Leu Thr Arg Arg Gly Leu Tyr Leu Ala Phe His Asn	
175 180 185	
ccg ggt gcc tgt gtg gcc ctg gtg tct gtc cgg gtc ttc tac cag cgc	628
Pro Gly Ala Cys Val Ala Leu Val Ser Val Arg Val Phe Tyr Gln Arg	
190 195 200	
tgt cct gag acc ctg aat ggc ttg gcc caa ttc cca gac act ctg cct	676
Cys Pro Glu Thr Leu Asn Gly Leu Ala Gln Phe Pro Asp Thr Leu Pro	
205 210 215	
ggc ccc gct ggg ttg gtg gaa gtg gcg ggg acc tgc ttg ccc cac gcg	724
Gly Pro Ala Gly Leu Val Glu Val Ala Gly Thr Cys Leu Pro His Ala	
220 225 230 235	
cgg gcc agc ccc agg ccc tca ggt gca ccc cgc atg cac tgc agc cct	772
Arg Ala Ser Pro Arg Pro Ser Gly Ala Pro Arg Met His Cys Ser Pro	
240 245 250	
gat ggc gag tgg ctg gtg cct gta gga cgg tgc cac tgt gag cct ggc	820
Asp Gly Glu Trp Leu Val Pro Val Gly Arg Cys His Cys Glu Pro Gly	
255 260 265	

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tat gag gaa ggt ggc agt ggc gaa gca tgt gtt gcc tgc cct agc ggc	868
Tyr Glu Glu Gly Gly Ser Gly Glu Ala Cys Val Ala Cys Pro Ser Gly	
270 275 280	
tcc tac cgg atg gac atg gac aca ccc cat tgt ctc acg tgc ccc cag	916
Ser Tyr Arg Met Asp Met Asp Thr Pro His Cys Leu Thr Cys Pro Gln	
285 290 295	
cag agc act gct gag tct gag ggg gcc acc atc tgt acc tgt gag agc	964
Gln Ser Thr Ala Glu Ser Glu Gly Ala Thr Ile Cys Thr Cys Glu Ser	
300 305 310 315	
ggc cat tac aga gct ccc ggg gag ggc ccc cag gtg gca tgc aca ggt	1012
Gly His Tyr Arg Ala Pro Gly Glu Gly Pro Gln Val Ala Cys Thr Gly	
320 325 330	
ccc ccc tcg gcc ccc cga aac ctg agc ttc tct gcc tca ggg act cag	1060
Pro Pro Ser Ala Pro Arg Asn Leu Ser Phe Ser Ala Ser Gly Thr Gln	
335 340 345	
ctc tcc ctg cgt tgg gaa ccc cca gca gat acg ggg gga cgc cag gat	1108
Leu Ser Leu Arg Trp Glu Pro Pro Ala Asp Thr Gly Gly Arg Gln Asp	
350 355 360	
gtc aga tac agt gtg agg tgt tcc cag tgt cag ggc aca gca cag gac	1156
Val Arg Tyr Ser Val Arg Cys Ser Gln Cys Gln Gly Thr Ala Gln Asp	
365 370 375	
ggg ggg ccc tgc cag ccc tgt ggg gtg ggc gtg cac ttc tcg ccg ggg	1204
Gly Gly Pro Cys Gln Pro Cys Gly Val Gly Val His Phe Ser Pro Gly	
380 385 390 395	
gcc cgg ggg ctc acc aca cct gca gtg cat gtc aat ggc ctt gaa cct	1252
Ala Arg Gly Leu Thr Thr Pro Ala Val His Val Asn Gly Leu Glu Pro	
400 405 410	
tat gcc aac tac acc ttt aat gtg gaa gcc caa aat gga gtg tca ggg	1300
Tyr Ala Asn Tyr Thr Phe Asn Val Glu Ala Gln Asn Gly Val Ser Gly	
415 420 425	
ctg ggc agc tct ggc cat gcc agc acc tca gtc agc atc agc atg ggg	1348
Leu Gly Ser Ser Gly His Ala Ser Thr Ser Val Ser Ile Ser Met Gly	
430 435 440	
cat gca ggt gag agg ctg aga ggg gct ggg aca ggg acc tgg tgg aga	1396
His Ala Gly Glu Arg Leu Arg Gly Ala Gly Thr Gly Thr Trp Trp Arg	
445 450 455	
cag aag ggc tta aga cca cag aac aaa ctg atg ggc agg aag cca tag	1444
Gln Lys Gly Leu Arg Pro Gln Asn Lys Leu Met Gly Arg Lys Pro *	
460 465 470	
aaaagttaact aagggttatctt ccttttttctt tacatatcca accttatccc tctggacccc	1504
cagagtcact gtcaggcctg tctctgagac tgggtgaagaa agaaccgagg caactagagc	1564
tgacctgggc ggggtcccgg ccccgaaagcc ctggggcgaa cctgacctat gagctgcacg	1624
tgctgaacca ggatgaagaa cggtagcaga tggttctaga acccaggggc ttgctgaca	1683

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<210> 149  
 <211> 474  
 <212> PRT  
 <213> Homo Sapiens

<400> 149  
 Met Glu Arg Arg Trp Pro Leu Gly Leu Gly Leu Val Leu Leu Leu Cys  
 1 5 10 15  
 Ala Pro Leu Pro Pro Gly Ala Arg Ala Lys Glu Val Thr Leu Met Asp  
 20 25 30  
 Thr Ser Lys Ala Gln Gly Glu Leu Gly Trp Leu Leu Asp Pro Pro Lys  
 35 40 45  
 Asp Gly Trp Ser Glu Gln Gln Gln Ile Leu Asn Gly Thr Pro Leu Tyr  
 50 55 60  
 Met Tyr Gln Asp Cys Pro Met Gln Gly Arg Arg Asp Thr Asp His Trp  
 65 70 75 80  
 Leu Arg Ser Asn Trp Ile Tyr Arg Gly Glu Glu Ala Ser Arg Val His  
 85 90 95  
 Val Glu Leu Gln Phe Thr Val Arg Asp Cys Lys Ser Phe Pro Gly Gly  
 100 105 110  
 Ala Gly Pro Leu Gly Cys Lys Glu Thr Phe Asn Leu Leu Tyr Met Glu  
 115 120 125  
 Ser Asp Gln Asp Val Gly Ile Gln Leu Arg Arg Pro Leu Phe Gln Lys  
 130 135 140  
 Val Thr Thr Val Ala Ala Asp Gln Ser Phe Thr Ile Arg Asp Leu Val  
 145 150 155 160  
 Ser Gly Ser Val Lys Leu Asn Val Glu Arg Cys Ser Leu Gly Arg Leu  
 165 170 175  
 Thr Arg Arg Gly Leu Tyr Leu Ala Phe His Asn Pro Gly Ala Cys Val  
 180 185 190  
 Ala Leu Val Ser Val Arg Val Phe Tyr Gln Arg Cys Pro Glu Thr Leu  
 195 200 205  
 Asn Gly Leu Ala Gln Phe Pro Asp Thr Leu Pro Gly Pro Ala Gly Leu  
 210 215 220  
 Val Glu Val Ala Gly Thr Cys Leu Pro His Ala Arg Ala Ser Pro Arg  
 225 230 235 240  
 Pro Ser Gly Ala Pro Arg Met His Cys Ser Pro Asp Gly Glu Trp Leu  
 245 250 255  
 Val Pro Val Gly Arg Cys His Cys Glu Pro Gly Tyr Glu Glu Gly Gly  
 260 265 270  
 Ser Gly Glu Ala Cys Val Ala Cys Pro Ser Gly Ser Tyr Arg Met Asp  
 275 280 285  
 Met Asp Thr Pro His Cys Leu Thr Cys Pro Gln Gln Ser Thr Ala Glu  
 290 295 300  
 Ser Glu Gly Ala Thr Ile Cys Thr Cys Glu Ser Gly His Tyr Arg Ala  
 305 310 315 320  
 Pro Gly Glu Gly Pro Gln Val Ala Cys Thr Gly Pro Pro Ser Ala Pro  
 325 330 335  
 Arg Asn Leu Ser Phe Ser Ala Ser Gly Thr Gln Leu Ser Leu Arg Trp  
 340 345 350  
 Glu Pro Pro Ala Asp Thr Gly Gly Arg Gln Asp Val Arg Tyr Ser Val  
 355 360 365  
 Arg Cys Ser Gln Cys Gln Gly Thr Ala Gln Asp Gly Gly Pro Cys Gln  
 370 375 380  
 Pro Cys Gly Val Gly Val His Phe Ser Pro Gly Ala Arg Gly Leu Thr

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385					390					395				400	
Thr	Pro	Ala	Val	His	Val	Asn	Gly	Leu	Glu	Pro	Tyr	Ala	Asn	Tyr	Thr
				405					410					415	
Phe	Asn	Val	Glu	Ala	Gln	Asn	Gly	Val	Ser	Gly	Leu	Gly	Ser	Ser	Gly
			420					425					430		
His	Ala	Ser	Thr	Ser	Val	Ser	Ile	Ser	Met	Gly	His	Ala	Gly	Glu	Arg
		435					440					445			
Leu	Arg	Gly	Ala	Gly	Thr	Gly	Thr	Trp	Trp	Arg	Gln	Lys	Gly	Leu	Arg
	450					455					460				
Pro	Gln	Asn	Lys	Leu	Met	Gly	Arg	Lys	Pro						
465					470										

&lt;210&gt; 150

&lt;211&gt; 1375

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (20)...(955)

&lt;400&gt; 150

caggtcccgg	cccggagct	atg	gag	cgg	cgc	tgg	ccc	ctg	ggg	cta	ggg	ctg	52			
		Met	Glu	Arg	Arg	Trp	Pro	Leu	Gly	Leu	Gly	Leu				
		1				5						10				
gtg	ctg	ctg	ctc	tgc	gcc	ccg	ctg	ccc	ccg	ggg	gcg	cgc	gcc	aag	gaa	100
Val	Leu	Leu	Leu	Cys	Ala	Pro	Leu	Pro	Pro	Gly	Ala	Arg	Ala	Lys	Glu	
			15					20					25			
gtt	act	ctg	atg	gac	aca	agc	aag	gca	cag	gga	gag	ctg	ggc	tgg	ctg	148
Val	Thr	Leu	Met	Asp	Thr	Ser	Lys	Ala	Gln	Gly	Glu	Leu	Gly	Trp	Leu	
			30				35					40				
ctg	gat	ccc	cca	aaa	gat	ggg	tgg	agt	gaa	cag	caa	cag	ata	ctg	aat	196
Leu	Asp	Pro	Pro	Lys	Asp	Gly	Trp	Ser	Glu	Gln	Gln	Gln	Ile	Leu	Asn	
	45					50					55					
ggg	aca	ccc	ctg	tac	atg	tac	cag	gac	tgc	cca	atg	caa	gga	cgc	aga	244
Gly	Thr	Pro	Leu	Tyr	Met	Tyr	Gln	Asp	Cys	Pro	Met	Gln	Gly	Arg	Arg	
	60				65				70						75	
gac	act	gac	cac	tgg	ctt	cgc	tcc	aat	tgg	atc	tac	cgc	ggg	gag	gag	292
Asp	Thr	Asp	His	Trp	Leu	Arg	Ser	Asn	Trp	Ile	Tyr	Arg	Gly	Glu	Glu	
			80						85					90		
gct	tcc	cgc	gtc	cac	gtg	gag	ctg	cag	ttc	acc	gtg	cgg	gac	tgc	aag	340
Ala	Ser	Arg	Val	His	Val	Glu	Leu	Gln	Phe	Thr	Val	Arg	Asp	Cys	Lys	
			95					100					105			
agt	ttc	cct	ggg	gga	gcc	ggg	cct	ctg	ggc	tgc	aag	gag	acc	ttc	aac	388
Ser	Phe	Pro	Gly	Gly	Ala	Gly	Pro	Leu	Gly	Cys	Lys	Glu	Thr	Phe	Asn	
		110				115						120				
ctt	ctg	tac	atg	gag	agt	gac	cag	gat	gtg	ggc	att	cag	ctc	cga	cgg	436

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Leu	Leu	Tyr	Met	Glu	Ser	Asp	Gln	Asp	Val	Gly	Ile	Gln	Leu	Arg	Arg		
125						130					135						
ccc	ttg	ttc	cag	aag	gta	acc	acg	gtg	gct	gca	gac	cag	agc	ttc	acc	484	
Pro	Leu	Phe	Gln	Lys	Val	Thr	Thr	Val	Ala	Ala	Asp	Gln	Ser	Phe	Thr		
140					145					150					155		
att	cga	gac	ctt	gtg	tct	ggc	tcc	gtg	aag	ctg	aat	gtg	gag	cgc	tgc	532	
Ile	Arg	Asp	Leu	Val	Ser	Gly	Ser	Val	Lys	Leu	Asn	Val	Glu	Arg	Cys		
				160					165						170		
tct	ctg	ggc	cgc	ctg	acc	cgc	cgt	ggc	ctc	tac	ctc	gct	ttc	cac	aac	580	
Ser	Leu	Gly	Arg	Leu	Thr	Arg	Arg	Gly	Leu	Tyr	Leu	Ala	Phe	His	Asn		
			175					180						185			
ccg	ggt	gcc	tgt	gtg	gcc	ctg	gtg	tct	gtc	cgg	gtc	ttc	tac	cag	cgc	628	
Pro	Gly	Ala	Cys	Val	Ala	Leu	Val	Ser	Val	Arg	Val	Phe	Tyr	Gln	Arg		
		190					195					200					
tgt	cct	gag	acc	ctg	aat	ggc	ttg	gcc	caa	ttc	cca	gac	act	ctg	cct	676	
Cys	Pro	Glu	Thr	Leu	Asn	Gly	Leu	Ala	Gln	Phe	Pro	Asp	Thr	Leu	Pro		
	205					210					215						
ggc	ccc	gct	ggg	ttg	gtg	gaa	gtg	gcg	ggg	acc	tgc	ttg	ccc	cac	gcg	724	
Gly	Pro	Ala	Gly	Leu	Val	Glu	Val	Ala	Gly	Thr	Cys	Leu	Pro	His	Ala		
	220				225					230					235		
cgg	gcc	agc	ccc	agg	ccc	tca	ggt	gca	ccc	cgc	atg	cac	tgc	agc	cct	772	
Arg	Ala	Ser	Pro	Arg	Pro	Ser	Gly	Ala	Pro	Arg	Met	His	Cys	Ser	Pro		
				240					245					250			
gat	ggc	gag	tgg	ctg	gtg	cct	gta	gga	cgg	tgc	cac	tgt	gag	cct	ggc	820	
Asp	Gly	Glu	Trp	Leu	Val	Pro	Val	Gly	Arg	Cys	His	Cys	Glu	Pro	Gly		
			255					260					265				
tat	gag	gaa	ggt	ggc	agt	ggc	gaa	gca	tgt	ggt	ggt	aag	aac	gga	ggc	868	
Tyr	Glu	Glu	Gly	Gly	Ser	Gly	Glu	Ala	Cys	Val	Gly	Lys	Asn	Gly	Gly		
		270					275					280					
ggt	gag	aac	ctg	agg	aac	cac	tcg	gga	gga	ttg	cag	gag	tac	ccc	ggc	916	
Gly	Glu	Asn	Leu	Arg	Asn	His	Ser	Gly	Gly	Leu	Gln	Glu	Tyr	Pro	Gly		
		285				290					295						
aga	gaa	gga	ggc	cag	tgc	tcc	gcc	tca	gtg	ggt	ttt	taa	cctgagtgct			965	
Arg	Glu	Gly	Gly	Gln	Cys	Ser	Ala	Ser	Val	Gly	Phe	*					
	300				305					310							
ccagagcagc	ggacacacac	atgcagagat	gtttccagta	gaagggattg	gggcaggaag	1025											
gggtggtggt	ggttctgcct	gtaaaaacat	ttacagaacc	actgctctgc	tgcgttctct	1085											
ctccagcctg	ccctagcggc	tcctaccgga	tggacatgga	cacaccccat	tgtctcacgt	1145											
gccccagca	gagcactgct	gagtcctgagg	gggccaccat	ctgtacctgt	gagagcggcc	1205											
attacagagc	tcccggggag	ggccccagg	tggcatgcac	agagtcactg	tcaggcctgt	1265											
ctctgagact	ggtgaagaaa	gaaccgaggc	aactagagct	gacctgggcg	gggtcccggc	1325											
cccgaagccc	tggggcgaaac	ctgacctatg	agctgcacgt	gctgaaccag		1375											

&lt;210&gt; 151

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&lt;211&gt; 311

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 151

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Met Glu Arg Arg Trp Pro Leu Gly Leu Gly Leu Val Leu Leu Cys
 1      5      10      15
Ala Pro Leu Pro Gly Ala Arg Ala Lys Glu Val Thr Leu Met Asp
 20      25      30
Thr Ser Lys Ala Gln Gly Glu Leu Gly Trp Leu Leu Asp Pro Pro Lys
 35      40      45
Asp Gly Trp Ser Glu Gln Gln Ile Leu Asn Gly Thr Pro Leu Tyr
 50      55      60
Met Tyr Gln Asp Cys Pro Met Gln Gly Arg Arg Asp Thr Asp His Trp
 65      70      75      80
Leu Arg Ser Asn Trp Ile Tyr Arg Gly Glu Glu Ala Ser Arg Val His
 85      90      95
Val Glu Leu Gln Phe Thr Val Arg Asp Cys Lys Ser Phe Pro Gly Gly
 100     105     110
Ala Gly Pro Leu Gly Cys Lys Glu Thr Phe Asn Leu Leu Tyr Met Glu
 115     120     125
Ser Asp Gln Asp Val Gly Ile Gln Leu Arg Arg Pro Leu Phe Gln Lys
 130     135     140
Val Thr Thr Val Ala Ala Asp Gln Ser Phe Thr Ile Arg Asp Leu Val
 145     150     155     160
Ser Gly Ser Val Lys Leu Asn Val Glu Arg Cys Ser Leu Gly Arg Leu
 165     170     175
Thr Arg Arg Gly Leu Tyr Leu Ala Phe His Asn Pro Gly Ala Cys Val
 180     185     190
Ala Leu Val Ser Val Arg Val Phe Tyr Gln Arg Cys Pro Glu Thr Leu
 195     200     205
Asn Gly Leu Ala Gln Phe Pro Asp Thr Leu Pro Gly Pro Ala Gly Leu
 210     215     220
Val Glu Val Ala Gly Thr Cys Leu Pro His Ala Arg Ala Ser Pro Arg
 225     230     235     240
Pro Ser Gly Ala Pro Arg Met His Cys Ser Pro Asp Gly Glu Trp Leu
 245     250     255
Val Pro Val Gly Arg Cys His Cys Glu Pro Gly Tyr Glu Glu Gly Gly
 260     265     270
Ser Gly Glu Ala Cys Val Gly Lys Asn Gly Gly Gly Glu Asn Leu Arg
 275     280     285
Asn His Ser Gly Gly Leu Gln Glu Tyr Pro Gly Arg Glu Gly Gly Gln
 290     295     300
Cys Ser Ala Ser Val Gly Phe
 305     310

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&lt;210&gt; 152

&lt;211&gt; 1511

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (20) ... (1492)

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&lt;400&gt; 152

```

caggtcccgg cccggagct atg gag cgg cgc tgg ccc ctg ggg cta ggg ctg 52
      Met Glu Arg Arg Trp Pro Leu Gly Leu Gly Leu
      1             5             10

gtg ctg ctg ctc tgc gcc ccg ctg ccc ccg ggg gcg cgc gcc aag gaa 100
Val Leu Leu Leu Cys Ala Pro Leu Pro Pro Gly Ala Arg Ala Lys Glu
      15             20             25

gtt act ctg atg gac aca agc aag gca cag gga gag ctg ggc tgg ctg 148
Val Thr Leu Met Asp Thr Ser Lys Ala Gln Gly Glu Leu Gly Trp Leu
      30             35             40

ctg gat ccc cca aaa gat ggg tgg agt gaa cag caa cag ata ctg aat 196
Leu Asp Pro Pro Lys Asp Gly Trp Ser Glu Gln Gln Gln Ile Leu Asn
      45             50             55

ggg aca ccc ctg tac atg tac cag gac tgc cca atg caa gga cgc aga 244
Gly Thr Pro Leu Tyr Met Tyr Gln Asp Cys Pro Met Gln Gly Arg Arg
      60             65             70             75

gac act gac cac tgg ctt cgc tcc aat tgg atc tac cgc ggg gag gag 292
Asp Thr Asp His Trp Leu Arg Ser Asn Trp Ile Tyr Arg Gly Glu Glu
      80             85             90

gct tcc cgc gtc cac gtg gag ctg cag ttc acc gtg cgg gac tgc aag 340
Ala Ser Arg Val His Val Glu Leu Gln Phe Thr Val Arg Asp Cys Lys
      95             100             105

agt ttc cct ggg gga gcc ggg cct ctg ggc tgc aag gag acc ttc aac 388
Ser Phe Pro Gly Gly Ala Gly Pro Leu Gly Cys Lys Glu Thr Phe Asn
      110             115             120

ctt ctg tac atg gag agt gac cag gat gtg ggc att cag ctc cga cgg 436
Leu Leu Tyr Met Glu Ser Asp Gln Asp Val Gly Ile Gln Leu Arg Arg
      125             130             135

ccc ttg ttc cag aag gta acc acg gtg gct gca gac cag agc ttc acc 484
Pro Leu Phe Gln Lys Val Thr Thr Val Ala Ala Asp Gln Ser Phe Thr
      140             145             150             155

att cga gac ctt gtg tct ggc tcc gtg aag ctg aat gtg gag cgc tgc 532
Ile Arg Asp Leu Val Ser Gly Ser Val Lys Leu Asn Val Glu Arg Cys
      160             165             170

tct ctg ggc cgc ctg acc cgc cgt ggc ctc tac ctc gct ttc cac aac 580
Ser Leu Gly Arg Leu Thr Arg Arg Gly Leu Tyr Leu Ala Phe His Asn
      175             180             185

ccg ggt gcc tgt gtg gcc ctg gtg tct gtc cgg gtc ttc tac cag cgc 628
Pro Gly Ala Cys Val Ala Leu Val Ser Val Arg Val Phe Tyr Gln Arg
      190             195             200

tgt cct gag acc ctg aat ggc ttg gcc caa ttc cca gac act ctg cct 676
Cys Pro Glu Thr Leu Asn Gly Leu Ala Gln Phe Pro Asp Thr Leu Pro
      205             210             215

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ggc ccc gct ggg ttg gtg gaa gtg gcg ggg acc tgc ttg ccc cac gcg	724
Gly Pro Ala Gly Leu Val Glu Val Ala Gly Thr Cys Leu Pro His Ala	
220 225 230 235	
cgg gcc agc ccc agg ccc tca ggt gca ccc cgc atg cac tgc agc cct	772
Arg Ala Ser Pro Arg Pro Ser Gly Ala Pro Arg Met His Cys Ser Pro	
240 245 250	
gat ggc gag tgg ctg gtg cct gta gga cgg tgc cac tgt gag cct ggc	820
Asp Gly Glu Trp Leu Val Pro Val Gly Arg Cys His Cys Glu Pro Gly	
255 260 265	
tat gag gaa ggt ggc agt ggc gaa gca tgt gtt gcc tgc cct agc ggc	868
Tyr Glu Glu Gly Gly Ser Gly Glu Ala Cys Val Ala Cys Pro Ser Gly	
270 275 280	
tcc tac cgg atg gac atg gac aca ccc cat tgt ctc acg tgc ccc cag	916
Ser Tyr Arg Met Asp Met Asp Thr Pro His Cys Leu Thr Cys Pro Gln	
285 290 295	
cag agc act gct gag tct gag ggg gcc acc atc tgt acc tgt gag agc	964
Gln Ser Thr Ala Glu Ser Glu Gly Ala Thr Ile Cys Thr Cys Glu Ser	
300 305 310 315	
ggc cat tac aga gct ccc ggg gag ggc ccc cag gtg gca tgc aca ggt	1012
Gly His Tyr Arg Ala Pro Gly Glu Gly Pro Gln Val Ala Cys Thr Gly	
320 325 330	
ccc ccc tcg gcc ccc cga aac ctg agc ttc tct gcc tca ggg act cag	1060
Pro Pro Ser Ala Pro Arg Asn Leu Ser Phe Ser Ala Ser Gly Thr Gln	
335 340 345	
ctc tcc ctg cgt tgg gaa ccc cca gca gat acg ggg gga cgc cag gat	1108
Leu Ser Leu Arg Trp Glu Pro Pro Ala Asp Thr Gly Gly Arg Gln Asp	
350 355 360	
gtc aga tac agt gtg agg tgt tcc cag tgt cag ggc aca gca cag gac	1156
Val Arg Tyr Ser Val Arg Cys Ser Gln Cys Gln Gly Thr Ala Gln Asp	
365 370 375	
ggg ggg ccc tgc cag ccc tgt ggg gtg ggc gtg cac ttc tcg ccg ggg	1204
Gly Gly Pro Cys Gln Pro Cys Gly Val Gly Val His Phe Ser Pro Gly	
380 385 390 395	
gcc cgg ggg ctc acc aca cct gca gtg cat gtc aat ggc ctt gaa cct	1252
Ala Arg Gly Leu Thr Thr Pro Ala Val His Val Asn Gly Leu Glu Pro	
400 405 410	
tat gcc aac tac acc ttt aat gtg gaa gcc caa aat gga gtg tca ggg	1300
Tyr Ala Asn Tyr Thr Phe Asn Val Glu Ala Gln Asn Gly Val Ser Gly	
415 420 425	
ctg ggc agc tct ggc cat gcc agc acc tca gtc agc atc agc atg ggg	1348
Leu Gly Ser Ser Gly His Ala Ser Thr Ser Val Ser Ile Ser Met Gly	
430 435 440	



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cat gca gat cca acc tta tcc ctc tgg acc ccc aga gtc act gtc agg 1396
His Ala Asp Pro Thr Leu Ser Leu Trp Thr Pro Arg Val Thr Val Arg
    445                450                455

cct gtc tct gag act ggt gaa gaa aga acc gag gca act aga gct gac 1444
Pro Val Ser Glu Thr Gly Glu Glu Arg Thr Glu Ala Thr Arg Ala Asp
460                465                470                475

ctg ggc ggg gtc ccg gcc ccg aag ccc tgg ggc gaa cct gac cta tga 1492
Leu Gly Gly Val Pro Ala Pro Lys Pro Trp Gly Glu Pro Asp Leu *
                480                485                490

gctgcacgtg ctgaaccag 1511

<210> 153
<211> 490
<212> PRT
<213> Homo Sapiens

<400> 153
Met Glu Arg Arg Trp Pro Leu Gly Leu Gly Leu Val Leu Leu Leu Cys
 1          5          10          15
Ala Pro Leu Pro Pro Gly Ala Arg Ala Lys Glu Val Thr Leu Met Asp
 20          25          30
Thr Ser Lys Ala Gln Gly Glu Leu Gly Trp Leu Leu Asp Pro Pro Lys
 35          40          45
Asp Gly Trp Ser Glu Gln Gln Gln Ile Leu Asn Gly Thr Pro Leu Tyr
 50          55          60
Met Tyr Gln Asp Cys Pro Met Gln Gly Arg Arg Asp Thr Asp His Trp
 65          70          75          80
Leu Arg Ser Asn Trp Ile Tyr Arg Gly Glu Glu Ala Ser Arg Val His
 85          90          95
Val Glu Leu Gln Phe Thr Val Arg Asp Cys Lys Ser Phe Pro Gly Gly
100          105          110
Ala Gly Pro Leu Gly Cys Lys Glu Thr Phe Asn Leu Leu Tyr Met Glu
115          120          125
Ser Asp Gln Asp Val Gly Ile Gln Leu Arg Arg Pro Leu Phe Gln Lys
130          135          140
Val Thr Thr Val Ala Ala Asp Gln Ser Phe Thr Ile Arg Asp Leu Val
145          150          155          160
Ser Gly Ser Val Lys Leu Asn Val Glu Arg Cys Ser Leu Gly Arg Leu
165          170          175
Thr Arg Arg Gly Leu Tyr Leu Ala Phe His Asn Pro Gly Ala Cys Val
180          185          190
Ala Leu Val Ser Val Arg Val Phe Tyr Gln Arg Cys Pro Glu Thr Leu
195          200          205
Asn Gly Leu Ala Gln Phe Pro Asp Thr Leu Pro Gly Pro Ala Gly Leu
210          215          220
Val Glu Val Ala Gly Thr Cys Leu Pro His Ala Arg Ala Ser Pro Arg
225          230          235          240
Pro Ser Gly Ala Pro Arg Met His Cys Ser Pro Asp Gly Glu Trp Leu
245          250          255
Val Pro Val Gly Arg Cys His Cys Glu Pro Gly Tyr Glu Glu Gly Gly
260          265          270
Ser Gly Glu Ala Cys Val Ala Cys Pro Ser Gly Ser Tyr Arg Met Asp

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Met	Asp	Thr	Pro	His	Cys	Leu	Thr	Cys	Pro	Gln	Gln	Ser	Thr	Ala	Glu	
	290					295					300					
Ser	Glu	Gly	Ala	Thr	Ile	Cys	Thr	Cys	Glu	Ser	Gly	His	Tyr	Arg	Ala	
305					310					315					320	
Pro	Gly	Glu	Gly	Pro	Gln	Val	Ala	Cys	Thr	Gly	Pro	Pro	Ser	Ala	Pro	
				325					330					335		
Arg	Asn	Leu	Ser	Phe	Ser	Ala	Ser	Gly	Thr	Gln	Leu	Ser	Leu	Arg	Trp	
			340					345					350			
Glu	Pro	Pro	Ala	Asp	Thr	Gly	Gly	Arg	Gln	Asp	Val	Arg	Tyr	Ser	Val	
			355				360				365					
Arg	Cys	Ser	Gln	Cys	Gln	Gly	Thr	Ala	Gln	Asp	Gly	Gly	Pro	Cys	Gln	
	370					375					380					
Pro	Cys	Gly	Val	Gly	Val	His	Phe	Ser	Pro	Gly	Ala	Arg	Gly	Leu	Thr	
385					390					395					400	
Thr	Pro	Ala	Val	His	Val	Asn	Gly	Leu	Glu	Pro	Tyr	Ala	Asn	Tyr	Thr	
				405					410					415		
Phe	Asn	Val	Glu	Ala	Gln	Asn	Gly	Val	Ser	Gly	Leu	Gly	Ser	Ser	Gly	
			420					425					430			
His	Ala	Ser	Thr	Ser	Val	Ser	Ile	Ser	Met	Gly	His	Ala	Asp	Pro	Thr	
		435					440					445				
Leu	Ser	Leu	Trp	Thr	Pro	Arg	Val	Thr	Val	Arg	Pro	Val	Ser	Glu	Thr	
	450					455					460					
Gly	Glu	Glu	Arg	Thr	Glu	Ala	Thr	Arg	Ala	Asp	Leu	Gly	Gly	Val	Pro	
465					470					475					480	
Ala	Pro	Lys	Pro	Trp	Gly	Glu	Pro	Asp	Leu							
				485					490							

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<220>  
<221> CDS  
<222> (20) ... (748)
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<400>	154
tgcgggcccgt cggccggcgc atg gcc ctg gat tat cta cta ctg ctc ctc ctg	52
Met Ala Leu Asp Tyr Leu Leu Leu Leu Leu Leu	
1 5 10	
gca tcc gca gtg gct gcg atg gaa gaa acg tta atg gac acc aga acg	100
Ala Ser Ala Val Ala Ala Met Glu Glu Thr Leu Met Asp Thr Arg Thr	
15 20 25	
gct act gca gag ctg ggc tgg acg gcc aat cct gcg tcc ggg tgg gaa	148
Ala Thr Ala Glu Leu Gly Trp Thr Ala Asn Pro Ala Ser Gly Trp Glu	
30 35 40	
gaa gtc agt ggc tac gat gaa aac ctg aac acc atc cgc acc tac cag	196
Glu Val Ser Gly Tyr Asp Glu Asn Leu Asn Thr Ile Arg Thr Tyr Gln	
45 50 55	
gtg tgc aat gtc ttc gag ccc aac cag aac aat tgg ctg ctc acc acc	244

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Val	Cys	Asn	Val	Phe	Glu	Pro	Asn	Gln	Asn	Asn	Trp	Leu	Leu	Thr	Thr		
60					65					70					75		
ttc	atc	aac	cgg	cgg	ggg	gcc	cat	cgc	atc	tac	aca	gag	atg	cgc	ttc	292	
Phe	Ile	Asn	Arg	Arg	Gly	Ala	His	Arg	Ile	Tyr	Thr	Glu	Met	Arg	Phe		
				80					85					90			
act	gtg	aga	gac	tgc	agc	agc	ctc	cct	aat	gtc	cca	gga	tcc	tgc	aag	340	
Thr	Val	Arg	Asp	Cys	Ser	Ser	Leu	Pro	Asn	Val	Pro	Gly	Ser	Cys	Lys		
			95					100					105				
gag	acc	ttc	aac	ttg	tat	tac	tat	gag	act	gac	tct	gtc	att	gcc	acc	388	
Glu	Thr	Phe	Asn	Leu	Tyr	Tyr	Tyr	Glu	Thr	Asp	Ser	Val	Ile	Ala	Thr		
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&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;308&gt; GenBank No. NM005424

&lt;309&gt; 2004-12-18

&lt;400&gt; 161

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&lt;211&gt; 3985

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

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&lt;309&gt; 2004-10-26

&lt;400&gt; 162

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&lt;211&gt; 5598

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&lt;213&gt; Homo Sapiens

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&lt;308&gt; GenBank No. NM002609

&lt;309&gt; 2004-10-26

&lt;400&gt; 163

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- 119 -

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&lt;210&gt; 164

&lt;211&gt; 3343

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. M34641

&lt;309&gt; 2001-12-14

&lt;400&gt; 164

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- 120 -

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&lt;210&gt; 165

&lt;211&gt; 3363

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. NM005232

&lt;309&gt; 2004-11-29

&lt;400&gt; 165

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- 121 -

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&lt;210&gt; 166

&lt;211&gt; 3865

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&lt;309&gt; 2004-11-15

&lt;400&gt; 166

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- 122 -

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 actgggtgta ccgaggagag gctgagcgta tcttcattga gctcaagttt actgtacgtg 420  
 actgcaacag cttccctggg ggcgccagct cctgcaagga gactttcaac ctctactatg 480  
 ccgagtcgga cctggactac ggcaccaact tccagaagcg cctgttcacc aagattgaca 540  
 ccattgcgcc cgatgagatc accgtcagca gcgacttcga ggcacgccac gtgaagctga 600  
 acgtggagga gcgctccgtg gggccgctca cccgcaaagg cttctacctg gccttcagg 660  
 atatcggtgc ctgtgtggca ctactctccg tccgtgtcta ctacgagaag tgccccgagc 720  
 cgctgcaggg cctggccccc ttccctgaga ccacgcggcg ctctgatgca cctccctgg 780  
 ccactgtggc cggcacctgt gtggaccatg ccgtgggtgcc accggggggg gaagagcccc 840  
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 ccacctctcg cgagtgtgag gaaggcttct tccgggcacc tcaggaccca gcgtcgatgc 1080  
 cttgcacacg acccccttcc gcccacact acctcacagc cgtgggcatg ggtgccaaag 1140  
 tggagctgcg ctggacgccc cctcaggaca gcggggggcg cgaggacatt gtctacagcg 1200  
 tcacctgcga acagtgtgag cccgagctcg ggggaatgcgg gccgtgtgag gccagtgtgc 1260  
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 gccgagtgtg gaagtacgag gtcacttacc gcaagaaggt aactcccaga ggggcggggc 1560  
 tggctctagc tgggcccaga gcaggggaca ggctggtcac actcgagtct agagggccct 1620  
 tcgaacaaaa actcatctca gaagaggatc tgaatatgca taccggtcat catcaccatc 1680  
 accattgagt ttaaaccgcg tgatcagcct cgactgtgcc t 1721

<210> 168  
 <211> 497  
 <212> PRT  
 <213> Homo Sapiens

<400> 168  
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 Ala Leu Ala Ala Ala Ala Ala Ala Gln Gly Lys Glu Val Val Leu Leu  
 20 25 30  
 Asp Phe Ala Ala Ala Gly Gly Glu Leu Gly Trp Leu Thr His Pro Tyr  
 35 40 45  
 Gly Lys Gly Trp Asp Leu Met Gln Asn Ile Met Asn Asp Met Pro Ile  
 50 55 60  
 Tyr Met Tyr Ser Val Cys Asn Val Met Ser Gly Asp Gln Asp Asn Trp  
 65 70 75 80  
 Leu Arg Thr Asn Trp Val Tyr Arg Gly Glu Ala Glu Arg Ile Phe Ile  
 85 90 95  
 Glu Leu Lys Phe Thr Val Arg Asp Cys Asn Ser Phe Pro Gly Gly Ala

			100					105					110			
Ser	Ser	Cys	Lys	Glu	Thr	Phe	Asn	Leu	Tyr	Tyr	Ala	Glu	Ser	Asp	Leu	
		115					120					125				
Asp	Tyr	Gly	Thr	Asn	Phe	Gln	Lys	Arg	Leu	Phe	Thr	Lys	Ile	Asp	Thr	
		130				135					140					
Ile	Ala	Pro	Asp	Glu	Ile	Thr	Val	Ser	Ser	Asp	Phe	Glu	Ala	Arg	His	
145				150						155					160	
Val	Lys	Leu	Asn	Val	Glu	Glu	Arg	Ser	Val	Gly	Pro	Leu	Thr	Arg	Lys	
			165						170						175	
Gly	Phe	Tyr	Leu	Ala	Phe	Gln	Asp	Ile	Gly	Ala	Cys	Val	Ala	Leu	Leu	
			180					185					190			
Ser	Val	Arg	Val	Tyr	Tyr	Glu	Lys	Cys	Pro	Glu	Pro	Leu	Gln	Gly	Leu	
		195					200					205				
Ala	His	Phe	Pro	Glu	Thr	Ile	Ala	Gly	Ser	Asp	Ala	Pro	Ser	Leu	Ala	
		210				215					220					
Thr	Val	Ala	Gly	Thr	Cys	Val	Asp	His	Ala	Val	Val	Pro	Pro	Gly	Gly	
225				230						235					240	
Glu	Glu	Pro	Arg	Met	His	Cys	Ala	Val	Asp	Gly	Glu	Trp	Leu	Val	Pro	
			245						250					255		
Ile	Gly	Gln	Cys	Leu	Cys	Gln	Ala	Gly	Tyr	Glu	Lys	Val	Glu	Asp	Ala	
			260					265					270			
Cys	Gln	Ala	Cys	Ser	Pro	Gly	Phe	Phe	Lys	Phe	Glu	Ala	Ser	Glu	Ser	
		275					280					285				
Pro	Cys	Leu	Glu	Cys	Pro	Glu	Arg	Thr	Leu	Pro	Ser	Pro	Glu	Gly	Ala	
		290				295					300					
Thr	Ser	Cys	Glu	Cys	Glu	Glu	Gly	Phe	Phe	Arg	Ala	Pro	Gln	Asp	Pro	
305				310						315					320	
Ala	Ser	Met	Pro	Cys	Thr	Arg	Pro	Pro	Ser	Ala	Pro	His	Tyr	Leu	Thr	
			325						330					335		
Ala	Val	Gly	Met	Gly	Ala	Lys	Val	Glu	Leu	Arg	Trp	Thr	Pro	Pro	Gln	
			340					345					350			
Asp	Ser	Gly	Arg	Glu	Asp	Ile	Val	Tyr	Ser	Val	Thr	Cys	Glu	Gln		
		355				360					365					
Cys	Trp	Pro	Glu	Ser	Gly	Glu	Cys	Gly	Pro	Cys	Glu	Ala	Ser	Val	Arg	
		370				375					380					
Tyr	Ser	Glu	Pro	Pro	His	Gly	Leu	Thr	Arg	Thr	Ser	Val	Thr	Val	Ser	
385				390						395					400	
Asp	Leu	Glu	Pro	His	Met	Asn	Tyr	Thr	Phe	Thr	Val	Glu	Ala	Arg	Asn	
			405						410					415		
Gly	Val	Ser	Gly	Leu	Val	Thr	Ser	Arg	Ser	Phe	Arg	Thr	Ala	Ser	Val	
			420					425					430			
Ser	Ile	Asn	Gln	Thr	Glu	Pro	Pro	Lys	Val	Arg	Leu	Glu	Gly	Arg	Ser	
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<210> 169
<211> 1353
<212> DNA
<213> Homo Sapiens
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<400> 169
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ctgctctgct gggcttcggt ggccgcagct ttggaagaga ccctgctgaa cacaaaattg 180
gaaactgctg atctgaagtg ggtgacattc cctcaggtgg acgggcagtg ggaggaactg 240
agcggcctgg atgaggaaca gcacagcgtg cgcacctacg aagtgtgtga cgtgcagcgt 300
gccccgggccc agggccactg gcttcgcaca ggttgggtcc cacggcgggg cgccgtccac 360
gtgtacgcca cgtgcgctt caccatgctc gagtgccgtt ccctgcctcg ggctgggcgc 420
tcctgcaagg agaccttcac cgtcttctac tatgagagcg atgcggacac ggccacggcc 480
ctcacgccag cctggatgga gaacccctac atcaaggtgg acacgggtgg cgcgagcat 540
ctcaccggga agcgccttg ggccgaggcc accgggaagg tgaatgtcaa gacgtgcgt 600
ctgggaccgc tcagcaaggc tggcttctac ctggccttcc aggaccaggg tgcctgcatg 660
gccctgctat ccctgcacct cttctacaaa aagtgcgccc agctgactgt gaacctgact 720
cgattcccgg agactgtgcc tcgggagctg gttgtgccc tggccggtag ctgcgtggtg 780
gatgccgtcc ccgcccctgg ccccagcccc agcctctact gccgtgagga tggccagtgg 840
gccgaacagc cggtcacggg ctgacagctg gctccgggtt tcgaggcagc tgaggggaac 900
accaagtgcc gagggcgccg aggggtcccag cagcgtgcgg ttctgaaga cgtcagaaaa 960
ccgggcagag ctgcgggggc tgaagcgggg agccagctac ctggtgcagg tacgggcgcg 1020
ctctgaggcc ggctacgggc ccttcggcca ggaacatcac agccagaccc aactggatga 1080
gagcgagggc tggcgggagc agctggccct gattgcgggc acggcagtcg tgggtgtggt 1140
cctggtcctg gtggtcattg tggtcgcagt tctctgcctc aggaagcaga gcaatgggag 1200
agaagcagaa tattcggaac aacacggaca gtatctcatc ggacatggta ctaaggtcta 1260
catcgacccc ttcaattatg aagaccctaa tgaggctgtg agggaatttg caaaagagat 1320
cgatgtctcc tacgtcaaga ttgaagaggt gat 1353

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&lt;210&gt; 170

&lt;211&gt; 306

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 170

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Met Glu Leu Arg Val Leu Leu Cys Trp Ala Ser Leu Ala Ala Leu
 1           5           10           15
Glu Glu Thr Leu Leu Asn Thr Lys Leu Glu Thr Ala Asp Leu Lys Trp
      20           25           30
Val Thr Phe Pro Gln Val Asp Gly Gln Trp Glu Glu Leu Ser Gly Leu
      35           40           45
Asp Glu Glu Gln His Ser Val Arg Thr Tyr Glu Val Cys Asp Val Gln
      50           55           60
Arg Ala Pro Gly Gln Ala His Trp Leu Arg Thr Gly Trp Val Pro Arg
      65           70           75           80
Arg Gly Ala Val His Val Tyr Ala Thr Leu Arg Phe Thr Met Leu Glu
      85           90           95
Cys Leu Ser Leu Pro Arg Ala Gly Arg Ser Cys Lys Glu Thr Phe Thr
      100          105          110
Val Phe Tyr Tyr Glu Ser Asp Ala Asp Thr Ala Thr Ala Leu Thr Pro
      115          120          125
Ala Trp Met Glu Asn Pro Tyr Ile Lys Val Asp Thr Val Ala Ala Glu
      130          135          140
His Leu Thr Arg Lys Arg Pro Gly Ala Glu Ala Thr Gly Lys Val Asn
      145          150          155          160
Val Lys Thr Leu Arg Leu Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu
      165          170          175
Ala Phe Gln Asp Gln Gly Ala Cys Met Ala Leu Leu Ser Leu His Leu
      180          185          190

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Phe Tyr Lys Lys Cys Ala Gln Leu Thr Val Asn Leu Thr Arg Phe Pro  
           195                          200                          205  
 Glu Thr Val Pro Arg Glu Leu Val Val Pro Val Ala Gly Ser Cys Val  
           210                          215                          220  
 Val Asp Ala Val Pro Ala Pro Gly Pro Ser Pro Ser Leu Tyr Cys Arg  
 225                          230                          235                          240  
 Glu Asp Gly Gln Trp Ala Glu Gln Pro Val Thr Gly Cys Ser Cys Ala  
                           245                          250                          255  
 Pro Gly Phe Glu Ala Ala Glu Gly Asn Thr Lys Cys Arg Gly Arg Arg  
                           260                          265                          270  
 Gly Ser Gln Gln Arg Ala Val Pro Glu Asp Val Arg Lys Pro Gly Arg  
                           275                          280                          285  
 Ala Ala Gly Ala Glu Ala Gly Ser Gln Leu Pro Gly Ala Gly Thr Gly  
                           290                          295                          300  
 Ala Leu  
 305

&lt;210&gt; 171

&lt;211&gt; 1813

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 171

actcagttcg gatcctaccc gagtgaggcg gcgccatgga gctccgggtg ctgctctgct 60  
 gggcttcggtt ggccgcagct ttggaagaga ccctgctgaa cacaaaattg gaaactgctg 120  
 atctgaagtg ggtgacattc cctcaggtgg acgggcagtg ggaggaactg agcggcctgg 180  
 atgaggaaca gcacagcgtg cgcacctacg aagtgtgtga cgtgcagcgt gccccggggc 240  
 agggccactg gcttcgcaca ggttgggtcc cacggcgggg cgccgtccac gtgtacgcca 300  
 cgctgcgctt caccatgctc gagtgcctgt ccctgcctcg ggctggggcg tcctgcaagg 360  
 agaccttcac cgtcttctac tatgagagcg atgcggacac ggccacggcc ctcacgccag 420  
 cctggatgga gaaccctac atcaaggtgg acacgggtggc cgcgagcat ctacccgga 480  
 agcgccttg ggccgaggcc accgggaagg tgaatgtcaa gacgtgctg ctgggaccgc 540  
 tcagcaaggc tggcttctac ctggccttcc aggaccaggg tgccctgcatg gccctgctat 600  
 ccctgcacct cttctacaaa aagtgcgccc agctgactgt gaacctgact cgattcccgg 660  
 agactgtgcc tcgggagctg gttgtgcccg tggccggtag ctgctggtg gatgccgtcc 720  
 ccgcccctgg cccagcccc agcctctact gccgtgagga tggccagtgg gccgaacagc 780  
 cggtcacggg ctgcagctgt gctccggggg tcgaggcagc tgaggggaac accaagtgcc 840  
 gagcctgtgc ccagggcacc ttcaagcccc tgtcaggaga agggctcctgc cagccatgcc 900  
 cagccaatag ccactctaac accattggat cagccgtctg ccagtgcgc gtcgggtact 960  
 tccgggcacg cacagacccc cgggggtgcac cctgcaccac ccctccttcg gctccgcgga 1020  
 gcgtgggttc ccgcctgaac ggctcctccc tgcacctgga atggagtgc cccctggagt 1080  
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 gcttgagcct ggcctgggct gttccccggg caccagtggt ggctgtgctg gactacgagg 1440  
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 aaaaccgggc agagctgcgg gggctgaagc ggggagccag ctacctgggtg cagagagcga 1560  
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 agaatatctg gacaaacacg gacagtatct catcggacat ggtactaagg tctacatcga 1740  
 cccttcact tatgaagacc ctaatgaggc tgtgagggaa ttgcaaaaag agatcgatgt 1800  
 ctctacgtc aag 1813



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<210> 172  
 <211> 516  
 <212> PRT  
 <213> Homo Sapiens

<400> 172  
 Met Glu Leu Arg Val Leu Leu Cys Trp Ala Ser Leu Ala Ala Ala Leu  
 1 5 10 15  
 Glu Glu Thr Leu Leu Asn Thr Lys Leu Glu Thr Ala Asp Leu Lys Trp  
 20 25 30  
 Val Thr Phe Pro Gln Val Asp Gly Gln Trp Glu Glu Leu Ser Gly Leu  
 35 40 45  
 Asp Glu Glu Gln His Ser Val Arg Thr Tyr Glu Val Cys Asp Val Gln  
 50 55 60  
 Arg Ala Pro Gly Gln Ala His Trp Leu Arg Thr Gly Trp Val Pro Arg  
 65 70 75 80  
 Arg Gly Ala Val His Val Tyr Ala Thr Leu Arg Phe Thr Met Leu Glu  
 85 90 95  
 Cys Leu Ser Leu Pro Arg Ala Gly Arg Ser Cys Lys Glu Thr Phe Thr  
 100 105 110  
 Val Phe Tyr Tyr Glu Ser Asp Ala Asp Thr Ala Thr Ala Leu Thr Pro  
 115 120 125  
 Ala Trp Met Glu Asn Pro Tyr Ile Lys Val Asp Thr Val Ala Ala Glu  
 130 135 140  
 His Leu Thr Arg Lys Arg Pro Gly Ala Glu Ala Thr Gly Lys Val Asn  
 145 150 155 160  
 Val Lys Thr Leu Arg Leu Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu  
 165 170 175  
 Ala Phe Gln Asp Gln Gly Ala Cys Met Ala Leu Leu Ser Leu His Leu  
 180 185 190  
 Phe Tyr Lys Lys Cys Ala Gln Leu Thr Val Asn Leu Thr Arg Phe Pro  
 195 200 205  
 Glu Thr Val Pro Arg Glu Leu Val Val Pro Val Ala Gly Ser Cys Val  
 210 215 220  
 Val Asp Ala Val Pro Ala Pro Gly Pro Ser Pro Ser Leu Tyr Cys Arg  
 225 230 235 240  
 Glu Asp Gly Gln Trp Ala Glu Gln Pro Val Thr Gly Cys Ser Cys Ala  
 245 250 255  
 Pro Gly Phe Glu Ala Ala Glu Gly Asn Thr Lys Cys Arg Ala Cys Ala  
 260 265 270  
 Gln Gly Thr Phe Lys Pro Leu Ser Gly Glu Gly Ser Cys Gln Pro Cys  
 275 280 285  
 Pro Ala Asn Ser His Ser Asn Thr Ile Gly Ser Ala Val Cys Gln Cys  
 290 295 300  
 Arg Val Gly Tyr Phe Arg Ala Arg Thr Asp Pro Arg Gly Ala Pro Cys  
 305 310 315 320  
 Thr Thr Pro Pro Ser Ala Pro Arg Ser Val Val Ser Arg Leu Asn Gly  
 325 330 335  
 Ser Ser Leu His Leu Glu Trp Ser Ala Pro Leu Glu Ser Gly Gly Arg  
 340 345 350  
 Glu Asp Leu Thr Tyr Ala Leu Arg Cys Arg Glu Cys Arg Pro Gly Gly  
 355 360 365  
 Ser Cys Ala Pro Cys Gly Gly Asp Leu Thr Phe Asp Pro Gly Pro Arg  
 370 375 380  
 Asp Leu Val Glu Pro Trp Val Val Val Arg Gly Leu Arg Pro Asp Phe  
 385 390 395 400

- 128 -

Thr Tyr Thr Phe Glu Val Thr Ala Leu Asn Gly Val Ser Ser Leu Ala  
                   405                  410                  415  
 Thr Gly Pro Val Pro Phe Glu Pro Val Asn Val Thr Thr Asp Arg Glu  
                   420                  425                  430  
 Val Pro Pro Ala Val Ser Asp Ile Arg Val Thr Arg Ser Ser Pro Ser  
                   435                  440                  445  
 Ser Leu Ser Leu Ala Trp Ala Val Pro Arg Ala Pro Ser Gly Ala Val  
                   450                  455                  460  
 Leu Asp Tyr Glu Val Lys Tyr His Glu Lys Gly Ala Glu Gly Pro Ser  
 465                  470                  475                  480  
 Ser Val Arg Phe Leu Lys Thr Ser Glu Asn Arg Ala Glu Leu Arg Gly  
                   485                  490                  495  
 Leu Lys Arg Gly Ala Ser Tyr Leu Val Gln Arg Ala Arg Ala Gly Gly  
                   500                  505                  510  
 Ser Ser Trp Pro  
                   515

&lt;210&gt; 173

&lt;211&gt; 1801

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 173

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 atctgaagtg ggtgacattc cctcaggtgg acgggcagtg ggaggaactg agcggcctgg 180  
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 agaccttcac cgtcttctac tatgagagcg atgcggacac ggccacggcc ctcacgccag 420  
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 agcgccctgg ggccgaggcc accgggaagg tgaatgtcaa gacgctgctg ctgggaccgc 540  
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 gcccttcggc caggaacatc acagccagac ccaactggat gagagcgagg gctggcggga 1560  
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 tgaagaccct aatgaggctg tgagggaatt tgcaaaagag atcgatgtct cctacgtcaa 1800  
 g 1801

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<210> 174  
 <211> 414  
 <212> PRT  
 <213> Homo Sapiens

<400> 174  
 Met Glu Leu Arg Val Leu Leu Cys Trp Ala Ser Leu Ala Ala Ala Leu  
 1 5 10 15  
 Glu Glu Thr Leu Leu Asn Thr Lys Leu Glu Thr Ala Asp Leu Lys Trp  
 20 25 30  
 Val Thr Phe Pro Gln Val Asp Gly Gln Trp Glu Glu Leu Ser Gly Leu  
 35 40 45  
 Asp Glu Glu Gln His Ser Val Arg Thr Tyr Glu Val Cys Asp Val Gln  
 50 55 60  
 Arg Ala Pro Gly Gln Ala His Trp Leu Arg Thr Gly Trp Val Pro Arg  
 65 70 75 80  
 Arg Gly Ala Val His Val Tyr Ala Thr Leu Arg Phe Thr Met Leu Glu  
 85 90 95  
 Cys Leu Ser Leu Pro Arg Ala Gly Arg Ser Cys Lys Glu Thr Phe Thr  
 100 105 110  
 Val Phe Tyr Tyr Glu Ser Asp Ala Asp Thr Ala Thr Ala Leu Thr Pro  
 115 120 125  
 Ala Trp Met Glu Asn Pro Tyr Ile Lys Val Asp Thr Val Ala Ala Glu  
 130 135 140  
 His Leu Thr Arg Lys Arg Pro Gly Ala Glu Ala Thr Gly Lys Val Asn  
 145 150 155 160  
 Val Lys Thr Leu Arg Leu Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu  
 165 170 175  
 Ala Phe Gln Asp Gln Gly Ala Cys Met Ala Leu Leu Ser Leu His Leu  
 180 185 190  
 Phe Tyr Lys Lys Cys Ala Gln Leu Thr Val Asn Leu Thr Arg Phe Pro  
 195 200 205  
 Glu Thr Val Pro Arg Glu Leu Val Val Pro Val Ala Gly Ser Cys Val  
 210 215 220  
 Val Asp Ala Val Pro Ala Pro Gly Pro Ser Pro Ser Leu Tyr Cys Arg  
 225 230 235 240  
 Glu Asp Gly Gln Trp Ala Glu Gln Pro Val Thr Gly Cys Ser Cys Ala  
 245 250 255  
 Pro Gly Phe Glu Ala Ala Glu Gly Asn Thr Lys Cys Arg Ala Cys Ala  
 260 265 270  
 Gln Gly Thr Phe Lys Pro Leu Ser Gly Glu Gly Ser Cys Gln Pro Cys  
 275 280 285  
 Pro Ala Asn Ser His Ser Asn Thr Ile Gly Ser Ala Val Cys Gln Cys  
 290 295 300  
 Arg Val Gly Tyr Phe Arg Ala Arg Thr Asp Pro Arg Gly Ala Pro Cys  
 305 310 315 320  
 Thr Thr Pro Pro Ser Ala Pro Arg Ser Val Val Ser Arg Leu Asn Gly  
 325 330 335  
 Ser Ser Leu His Leu Glu Trp Ser Ala Pro Leu Glu Ser Gly Gly Arg  
 340 345 350  
 Glu Asp Leu Thr Tyr Ala Leu Arg Cys Arg Glu Cys Arg Pro Gly Gly  
 355 360 365  
 Ser Cys Ala Pro Cys Gly Gly Asp Leu Thr Phe Asp Pro Gly Pro Arg  
 370 375 380  
 Asp Leu Val Glu Pro Trp Val Val Val Arg Gly Leu Arg Pro Asp Phe  
 385 390 395 400

- 130 -

Thr Tyr Thr Phe Glu Tyr Leu Leu Gln Cys Leu Thr Ser Gly  
 405 410

&lt;210&gt; 175

&lt;211&gt; 965

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 175

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atgtggagct ggaagtgcct cctcttcttg gctgtgctgg tcacagccac actctgcacc 60
gctaggccgt ccccgacctt gcctgaacaa gatgctctcc cctcctcgga ggatgatgat 120
gatgatgatg actcctcttc agaggagaaa gaaacagata acaccaaacc aaaccgtatg 180
cccgtagctc catattggac atccccagaa aagatggaaa agaaattgca tgcagtgccg 240
gctgccaaaga cagtgaagtt caaatgccct tccagtggga ccccaaacc cactgctgc 300
tggttggaaga atggcaaaga attcaaacct ggccacagaa ttggaggcta caaggtccgt 360
tatgccacct ggagcatcat aatggactct gtggtgccct ctgacaagg caactacacc 420
tgcattgttg agaattagta cggcagcatc aaccacacat accagctgga tgcgtggag 480
cgggtccctc accggcccat cctgcaagca ggggtgccc ccaacaaaac agtggccctg 540
ggtagcaacg tggagttcat gtgtaagggtg tacagtgacc cgcagccgca catccagtgg 600
ctaaagcaca tcgaggtgaa tgggagcaag attggcccgg acaacctgcc ttatgtccag 660
atcttgaaga ctgctggagt taataccacc gacaaagaga tggaggtgct tcacttaaga 720
aatgtctcct ttgaggacgc aggggagtat acgtgcttgg cgggtaactc tatcggactc 780
tcccatcact ctgcatggtt gaccgttctg gaaggtagac actgtaactt ctctctcga 840
tgtcctgccc tcgccacggg caccgggggga gcatgcattt ccaggcttgg ggagacacag 900
aggcaggaga gctggaagaa tgggctcctg cctgcctggg gccacatcct gccccagctt 965
tgagg

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&lt;210&gt; 176

&lt;211&gt; 320

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 176

```

Met Trp Ser Trp Lys Cys Leu Leu Phe Trp Ala Val Leu Val Thr Ala
1 5 10 15
Thr Leu Cys Thr Ala Arg Pro Ser Pro Thr Leu Pro Glu Gln Asp Ala
20 25 30
Leu Pro Ser Ser Glu Asp Asp Asp Asp Asp Ser Ser Ser Glu
35 40 45
Glu Lys Glu Thr Asp Asn Thr Lys Pro Asn Arg Met Pro Val Ala Pro
50 55 60
Tyr Trp Thr Ser Pro Glu Lys Met Glu Lys Lys Leu His Ala Val Pro
65 70 75 80
Ala Ala Lys Thr Val Lys Phe Lys Cys Pro Ser Ser Gly Thr Pro Asn
85 90 95
Pro Thr Leu Arg Trp Leu Glu Asn Gly Lys Glu Phe Lys Pro Gly His
100 105 110
Arg Ile Gly Gly Tyr Lys Val Arg Tyr Ala Thr Trp Ser Ile Ile Met
115 120 125
Asp Ser Val Val Pro Ser Asp Lys Gly Asn Tyr Thr Cys Ile Val Glu
130 135 140
Asn Glu Tyr Gly Ser Ile Asn His Thr Tyr Gln Leu Asp Val Val Glu
145 150 155 160
Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Lys
165 170 175

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Thr	Val	Ala	Leu	Gly	Ser	Asn	Val	Glu	Phe	Met	Cys	Lys	Val	Tyr	Ser
		180						185					190		
Asp	Pro	Gln	Pro	His	Ile	Gln	Trp	Leu	Lys	His	Ile	Glu	Val	Asn	Gly
		195					200					205			
Ser	Lys	Ile	Gly	Pro	Asp	Asn	Leu	Pro	Tyr	Val	Gln	Ile	Leu	Lys	Thr
	210					215					220				
Ala	Gly	Val	Asn	Thr	Thr	Asp	Lys	Glu	Met	Glu	Val	Leu	His	Leu	Arg
225					230					235					240
Asn	Val	Ser	Phe	Glu	Asp	Ala	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly	Asn
			245					250						255	
Ser	Ile	Gly	Leu	Ser	His	His	Ser	Ala	Trp	Leu	Thr	Val	Leu	Glu	Gly
		260						265					270		
Thr	His	Cys	Asn	Phe	Ser	Ser	Arg	Cys	Pro	Ala	Leu	Ala	Thr	Gly	Thr
	275						280					285			
Gly	Gly	Ala	Cys	Ile	Ser	Arg	Leu	Gly	Glu	Thr	Gln	Arg	Gln	Glu	Ser
	290					295					300				
Trp	Lys	Asn	Gly	Leu	Leu	Pro	Ala	Trp	Cys	His	Ile	Leu	Pro	Gln	Leu
305					310					315					320

&lt;210&gt; 177

&lt;211&gt; 801

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 177

```

atgggtcagct ggggtcgttt catctgcctg gtcgtgggtca ccatgggcaac cttgtccctg 60
gcccggccct ccttcagttt agttgaggat accacattag agccagaaga gccaccaacc 120
aaataccaaa tctctcaacc agaagtgtac gtggctgcgc cagggggagtc gctagagggtg 180
cgctgcctgt tgaaagatgc cgccgtgatc agttggacta aggatggggt gcacttggggg 240
cccaacaata ggacagtgtt tattggggag tacttgcaga taaagggcgc cagccctaga 300
gactccggcc tctatgcttg tactgccagt aggactgtag acagtgaaac ttgtacttc 360
atggtgaatg tcacagatgc catctcatcc ggagatgatg aggatgacac cgatgggtgcg 420
gaagattttg tcagtgcaga cagtaacaac aagagagcac catactggac caacacagaa 480
aagatggaaa agcgggtcca tgctgtgcct gcgggccaaca ctgtcaagtt tcgctgccc 540
gcccggggga acccaatgcc aacctgcgg tggctgaaaa acgggaagga gtttaagcag 600
gagcatcgca ttggaggcta caaggtaga aaccagcact ggagcctcat tatggaaagt 660
gtggtcccat ctgacaaggg aaattatacc tgtgtgggtg agaatgaata cgggtccatc 720
aatcacacgt accacctgga tggtgtgggt gagtctgcct ctctcgtgt ggcggctgca 780
taccagccca ttcttgcttg a                                     801

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&lt;210&gt; 178

&lt;211&gt; 266

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 178

Met	Val	Ser	Trp	Gly	Arg	Phe	Ile	Cys	Leu	Val	Val	Val	Thr	Met	Ala
1				5					10					15	
Thr	Leu	Ser	Leu	Ala	Arg	Pro	Ser	Phe	Ser	Leu	Val	Glu	Asp	Thr	Thr
			20					25					30		
Leu	Glu	Pro	Glu	Glu	Pro	Pro	Thr	Lys	Tyr	Gln	Ile	Ser	Gln	Pro	Glu
	35						40					45			
Val	Tyr	Val	Ala	Ala	Pro	Gly	Glu	Ser	Leu	Glu	Val	Arg	Cys	Leu	Leu
	50					55					60				
Lys	Asp	Ala	Ala	Val	Ile	Ser	Trp	Thr	Lys	Asp	Gly	Val	His	Leu	Gly

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65					70					75				80	
Pro	Asn	Asn	Arg	Thr	Val	Leu	Ile	Gly	Glu	Tyr	Leu	Gln	Ile	Lys	Gly
				85					90					95	
Ala	Thr	Pro	Arg	Asp	Ser	Gly	Leu	Tyr	Ala	Cys	Thr	Ala	Ser	Arg	Thr
			100					105					110		
Val	Asp	Ser	Glu	Thr	Trp	Tyr	Phe	Met	Val	Asn	Val	Thr	Asp	Ala	Ile
		115				120						125			
Ser	Ser	Gly	Asp	Asp	Glu	Asp	Asp	Thr	Asp	Gly	Ala	Glu	Asp	Phe	Val
	130					135					140				
Ser	Glu	Asn	Ser	Asn	Asn	Lys	Arg	Ala	Pro	Tyr	Trp	Thr	Asn	Thr	Glu
145					150					155					160
Lys	Met	Glu	Lys	Arg	Leu	His	Ala	Val	Pro	Ala	Ala	Asn	Thr	Val	Lys
			165						170					175	
Phe	Arg	Cys	Pro	Ala	Gly	Gly	Asn	Pro	Met	Pro	Thr	Met	Arg	Trp	Leu
			180					185					190		
Lys	Asn	Gly	Lys	Glu	Phe	Lys	Gln	Glu	His	Arg	Ile	Gly	Gly	Tyr	Lys
	195						200					205			
Val	Arg	Asn	Gln	His	Trp	Ser	Leu	Ile	Met	Glu	Ser	Val	Val	Pro	Ser
	210					215					220				
Asp	Lys	Gly	Asn	Tyr	Thr	Cys	Val	Val	Glu	Asn	Glu	Tyr	Gly	Ser	Ile
225					230					235					240
Asn	His	Thr	Tyr	His	Leu	Asp	Val	Val	Gly	Glu	Ser	Ala	Ser	Pro	Arg
				245					250					255	
Val	Ala	Ala	Ala	Tyr	Gln	Pro	Ile	Leu	Ala						
			260					265							

&lt;210&gt; 179

&lt;211&gt; 953

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 179

atgggtcagct	gggggtcgctt	catctgcctg	gtcgtgggtca	ccatggcaac	cttgtccctg	60
gccccggccct	ccttcagttt	agttgaggat	accacattag	agccagaaga	gccaccaacc	120
aaataccaaa	tctctcaacc	agaagtgtac	gtggctgcgc	caggggagtc	gctagagggtg	180
cgctgcctgt	tgaaagatgc	cgccgtgac	agttggacta	aggatggggg	gcacttggggg	240
cccaacaata	ggacagtgc	tattggggag	tacttgacaga	taaaggggcg	cacgcctaga	300
gactccggcc	tctatgcttg	tactgccagt	aggactgtag	acagtgaac	ttggtacttc	360
atgggtgaatg	tcacagatgc	catctcatcc	ggagatgatg	aggatgacac	cgatgggtgcg	420
gaagattttg	tcagtggagaa	cagtaacaac	aagagagcac	catactggac	caacacagaa	480
aagatggaaa	agcggctcca	tgctgtgcct	gcggccaaca	ctgtcaagtt	tcgctgcccc	540
gccggggggga	acccaatgcc	aaccatgcgg	tggttgaaaa	acgggaagga	gtttaagcag	600
gagcatcgca	ttggaggcta	caaggtagca	aaccagcact	ggagcctcat	tatggaaagt	660
gtgggtcccat	ctgacaaggg	aaattatacc	tggttggtgg	agaatgaata	cgggtccatc	720
aatcacacgt	accacctgga	tggtgtggag	cgatcgctc	accggcccat	cctccaagcc	780
ggactgcccg	caaatgcctc	cacagtgggc	ggaggagacg	tagagtttgt	ctgcaagggt	840
tacagtgatg	cccagcccca	catccagtgg	atcaagcacg	tgaaaaagaa	cggcagtaaa	900
tacggggccc	acgggctgcc	ctacctcaag	gttctcaagg	tgaggacttt	ctg	953

&lt;210&gt; 180

&lt;211&gt; 317

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 180

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```

Met Val Ser Trp Gly Arg Phe Ile Cys Leu Val Val Val Thr Met Ala
 1      5      10      15
Thr Leu Ser Leu Ala Arg Pro Ser Phe Ser Leu Val Glu Asp Thr Thr
      20      25      30
Leu Glu Pro Glu Glu Pro Pro Thr Lys Tyr Gln Ile Ser Gln Pro Glu
      35      40      45
Val Tyr Val Ala Ala Pro Gly Glu Ser Leu Glu Val Arg Cys Leu Leu
      50      55      60
Lys Asp Ala Ala Val Ile Ser Trp Thr Lys Asp Gly Val His Leu Gly
      65      70      75      80
Pro Asn Asn Arg Thr Val Leu Ile Gly Glu Tyr Leu Gln Ile Lys Gly
      85      90      95
Ala Thr Pro Arg Asp Ser Gly Leu Tyr Ala Cys Thr Ala Ser Arg Thr
      100      105      110
Val Asp Ser Glu Thr Trp Tyr Phe Met Val Asn Val Thr Asp Ala Ile
      115      120      125
Ser Ser Gly Asp Asp Glu Asp Asp Thr Asp Gly Ala Glu Asp Phe Val
      130      135      140
Ser Glu Asn Ser Asn Asn Lys Arg Ala Pro Tyr Trp Thr Asn Thr Glu
      145      150      155      160
Lys Met Glu Lys Arg Leu His Ala Val Pro Ala Ala Asn Thr Val Lys
      165      170      175
Phe Arg Cys Pro Ala Gly Gly Asn Pro Met Pro Thr Met Arg Trp Leu
      180      185      190
Lys Asn Gly Lys Glu Phe Lys Gln Glu His Arg Ile Gly Gly Tyr Lys
      195      200      205
Val Arg Asn Gln His Trp Ser Leu Ile Met Glu Ser Val Val Pro Ser
      210      215      220
Asp Lys Gly Asn Tyr Thr Cys Val Val Glu Asn Glu Tyr Gly Ser Ile
      225      230      235      240
Asn His Thr Tyr His Leu Asp Val Val Glu Arg Ser Pro His Arg Pro
      245      250      255
Ile Leu Gln Ala Gly Leu Pro Ala Asn Ala Ser Thr Val Val Gly Gly
      260      265      270
Asp Val Glu Phe Val Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile
      275      280      285
Gln Trp Ile Lys His Val Glu Lys Asn Gly Ser Lys Tyr Gly Pro Asp
      290      295      300
Gly Leu Pro Tyr Leu Lys Val Leu Lys Val Arg Thr Phe
      305      310      315

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&lt;210&gt; 181

&lt;211&gt; 844

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 181

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atggtcagct ggggtcgctt catctgcctg gtcgtgggtca ccatggcaac cttgtccctg 60
gcccgccct ccttcagttt agttgaggat atcacattag agccagaagg agcaccatac 120
tggaccaaca cagaaaagat ggaaaagcgg ctccatgctg tgccctgcggc caacactgtc 180
aagtttcgct gccagccgg ggggaaccca atgccaacca tgcggtggct gaaaaacggg 240
aaggagttta agcaggagca tcgcattgga ggctacaagg tacgaaacca gcactggagc 300
ctcattatgg aaagtgtggt cccatctgac aagggaatt atacctgtgt ggtggagaat 360
gaatacgggt ccatcaatca cacgtaccac ctggatgttg tggagcgatc gcctcaccgg 420
cccatcctcc aagccggact gccggcaaat gcctccacag tggtcggagg agacgtagag 480

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tttgtctgca aggtttacag tgatgccag cccacatcc agtggatcaa gcacgtggaa 540
aagaacggca gtaaatacgg gcccgcggg ctgccctacc tcaagggtct caaggccgcc 600
ggtgttaaca ccacggacaa agagattgag gttctctata ttcggaatgt aacttttgag 660
gacgctgggg aatatacgtg cttggcgggt aattctattg ggatatacctt tcactccgca 720
tggttgacag ttctgccagg tatatactgt tctttctctc tgggtttttt tcctttttct 780
tggttgactg ctataaaatt aacacagctt ctgttatcag aaatggcccc ttttatcctt 840
gcat

```

<210> 182  
 <211> 281  
 <212> PRT  
 <213> Homo Sapiens

```

<400> 182
Met Val Ser Trp Gly Arg Phe Ile Cys Leu Val Val Val Thr Met Ala
 1           5           10           15
Thr Leu Ser Leu Ala Arg Pro Ser Phe Ser Leu Val Glu Asp Ile Thr
      20           25           30
Leu Glu Pro Glu Gly Ala Pro Tyr Trp Thr Asn Thr Glu Lys Met Glu
      35           40           45
Lys Arg Leu His Ala Val Pro Ala Ala Asn Thr Val Lys Phe Arg Cys
      50           55           60
Pro Ala Gly Gly Asn Pro Met Pro Thr Met Arg Trp Leu Lys Asn Gly
      65           70           75           80
Lys Glu Phe Lys Gln Glu His Arg Ile Gly Tyr Lys Val Arg Asn
      85           90           95
Gln His Trp Ser Leu Ile Met Glu Ser Val Val Pro Ser Asp Lys Gly
      100          105          110
Asn Tyr Thr Cys Val Val Glu Asn Glu Tyr Gly Ser Ile Asn His Thr
      115          120          125
Tyr His Leu Asp Val Val Glu Arg Ser Pro His Arg Pro Ile Leu Gln
      130          135          140
Ala Gly Leu Pro Ala Asn Ala Ser Thr Val Val Gly Gly Asp Val Glu
      145          150          155          160
Phe Val Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Ile
      165          170          175
Lys His Val Glu Lys Asn Gly Ser Lys Tyr Gly Pro Asp Gly Leu Pro
      180          185          190
Tyr Leu Lys Val Leu Lys Ala Ala Gly Val Asn Thr Thr Asp Lys Glu
      195          200          205
Ile Glu Val Leu Tyr Ile Arg Asn Val Thr Phe Glu Asp Ala Gly Glu
      210          215          220
Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Ile Ser Phe His Ser Ala
      225          230          235          240
Trp Leu Thr Val Leu Pro Gly Ile Tyr Cys Ser Phe Ser Leu Gly Phe
      245          250          255
Phe Pro Phe Ser Trp Leu Thr Ala Ile Lys Leu Thr Gln Leu Leu Leu
      260          265          270
Ser Glu Met Ala Pro Phe Ile Leu Ala
      275          280

```

<210> 183  
 <211> 1191  
 <212> DNA  
 <213> Homo Sapiens



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<400> 183
atgggtcagct ggggtcgctt catctgcctg gtcgtgggtca ccatggcaac cttgtccctg 60
gcccgccct ccttcagttt agttgaggat accacattag agccagaaga gccaccaacc 120
aaataccaaa tctctcaacc agaagtgtac gtggctgctg caggggagtc gctagagggtg 180
cgctgcctgt tgaaagatgc cgccgtgatc agttggacta aggatggggg gactttgggg 240
cccaacaata ggacagtgc tattggggag tacttgaga taaagggcgc cagcgctaga 300
gactccggcc tctatgcttg tactgccagt aggactgtag acagtgaac ttggtacttc 360
atgggtgaatg tcacagatgc catctcatcc ggagatgatg aggatgacac cgatgggtgcg 420
gaagattttg tcagtgaaga cagtaacaac aagagagcac catactggac caacacagaa 480
aagacggaaa agcggctcca tgctgtgcct gcggccaaca ctgtcaagtt tcgctgcccc 540
gccgggggga acccaatgcc aaccatgcgg tggtgaaaa acgggaagga gtttaagcag 600
gagcatcgca ttggaggcta caaggtaga aaccagcact ggagcctcat tatggaaagt 660
gtgggtcccat ctgacaaggg aaattatacc tgtgtggttg agaatgaata cgggtccatc 720
aatcacacgt accacctgga tgttgtggag cgatcgctc accggcccat cctccaagcc 780
ggactgccgg caaatgcctc cacagtgggtc ggaggagacg tagagtttgt ctgcaagggt 840
tacagtgatg cccagcccc catccagtgg atcaagcac tggaaaagaa cggcagtaaa 900
tacgggcccc acgggctgcc ctacctcaag gttctcaagg ccgccggtgt taacaccacg 960
gacaaagaga ttgaggttct ctatatctcg aatgtaactt ttgaggacgc tggggaatat 1020
acgtgcttgg cgggtaattc tattgggata tcctttcact ctgcatggtt gacagttctg 1080
ccaggatatat actgttcttt ctctctgggt ttttttcct tttcttggtt gactgctata 1140
aaattaacac agcttctgtt atcagaaatg gcccctttta tccttgcata a 1191

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&lt;210&gt; 184

&lt;211&gt; 396

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 184

```

Met Val Ser Trp Gly Arg Phe Ile Cys Leu Val Val Val Thr Met Ala
1          5          10          15
Thr Leu Ser Leu Ala Arg Pro Ser Phe Ser Leu Val Glu Asp Thr Thr
          20          25          30
Leu Glu Pro Glu Glu Pro Pro Thr Lys Tyr Gln Ile Ser Gln Pro Glu
          35          40          45
Val Tyr Val Ala Ala Pro Gly Glu Ser Leu Glu Val Arg Cys Leu Leu
          50          55          60
Lys Asp Ala Ala Val Ile Ser Trp Thr Lys Asp Gly Val His Leu Gly
65          70          75          80
Pro Asn Asn Arg Thr Val Leu Ile Gly Glu Tyr Leu Gln Ile Lys Gly
          85          90          95
Ala Thr Pro Arg Asp Ser Gly Leu Tyr Ala Cys Thr Ala Ser Arg Thr
          100          105          110
Val Asp Ser Glu Thr Trp Tyr Phe Met Val Asn Val Thr Asp Ala Ile
          115          120          125
Ser Ser Gly Asp Asp Glu Asp Asp Thr Asp Gly Ala Glu Asp Phe Val
          130          135          140
Ser Glu Asn Ser Asn Asn Lys Arg Ala Pro Tyr Trp Thr Asn Thr Glu
145          150          155          160
Lys Thr Glu Lys Arg Leu His Ala Val Pro Ala Ala Asn Thr Val Lys
          165          170          175
Phe Arg Cys Pro Ala Gly Gly Asn Pro Met Pro Thr Met Arg Trp Leu
          180          185          190
Lys Asn Gly Lys Glu Phe Lys Gln Glu His Arg Ile Gly Gly Tyr Lys
          195          200          205
Val Arg Asn Gln His Trp Ser Leu Ile Met Glu Ser Val Val Pro Ser

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210	215	220
Asp Lys Gly Asn Tyr Thr Cys Val Val Glu Asn Glu Tyr Gly Ser Ile		
225	230	235
Asn His Thr Tyr His Leu Asp Val Val Glu Arg Ser Pro His Arg Pro		
	245	250
Ile Leu Gln Ala Gly Leu Pro Ala Asn Ala Ser Thr Val Val Gly Gly		
	260	265
Asp Val Glu Phe Val Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile		
	275	280
Gln Trp Ile Lys His Val Glu Lys Asn Gly Ser Lys Tyr Gly Pro Asp		
	290	295
Gly Leu Pro Tyr Leu Lys Val Leu Lys Ala Ala Gly Val Asn Thr Thr		
305	310	315
Asp Lys Glu Ile Glu Val Leu Tyr Ile Arg Asn Val Thr Phe Glu Asp		
	325	330
Ala Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Ile Ser Phe		
	340	345
His Ser Ala Trp Leu Thr Val Leu Pro Gly Ile Tyr Cys Ser Phe Ser		
	355	360
Leu Gly Phe Phe Pro Phe Ser Trp Leu Thr Ala Ile Lys Leu Thr Gln		
	370	375
Leu Leu Leu Ser Glu Met Ala Pro Phe Ile Leu Ala		
385	390	395

&lt;210&gt; 185

&lt;211&gt; 1240

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 185

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atgaaggccc ccgctgtgct tgcacctggc atcctcgtgc tcctgtttac cttggtgcag 60
aggagcaatg gggagtgtaa agaggcacta gcaaagtcog agatgaatgt gaatatgaag 120
tatcagcttc ccaacttcac cgcggaaaca cccatccaga atgtcattct acatgagcat 180
cacattttcc ttggtgccac taactacatt tatgttttaa atgaggaaga ctttcagaag 240
gttgtgagtg acaagactgg gcctgtgctg gaacacccag attgtttccc atgtcaggac 300
tgcagcagca aagccaatth atcaggagggt gtttggaaag ataacatcaa catggctcta 360
gttgtcgaca cctactatga tgatcaactc attagctgtg gcagcgtcaa cagagggacc 420
tgccagcgac atgtctttcc ccacaatcat actgctgata tacagtcgga ggttcactgc 480
atattctccc cacagataga agagcccagc cagtgtcctg actgtgtggt gagcgccctg 540
ggagccaaag tcctttcatc tgtaaaggac cggttcatca acttctttgt aggcaatacc 600
ataaattctt cttattttcc agatcatcca ttgcatcga tatcagttag aaggctaaag 660
gaaacgaaag atggttttat gtttttgacg gaccagtcct acattgatgt tttacctgag 720
ttcagagatt cttaccccat taagtatgtc catgcctttg aaagcaacaa ttttatttac 780
ttcttgacgg tccaaaggga aactctagat gctcagactt ttcacacaag aataatcagg 840
ttctgttcca taaactctgg attgcattcc tacatggaaa tgcctctgga gtgtattctc 900
acagaaaaga gaaaaagag atccacaaag aaggaagtgt taaatatact tcaggctgag 960
tatgtcagca agcctggggc ccagcttgct aggcaaatag gagccagcct gaatgatgac 1020
attcttttcg ggggtgttcg acaaagcaag ccagattctg ccgaaccaat ggatcgatct 1080
gccatgtgtg cattccctat caaatatgtc aacgacttct tcaacaagat cgtcaacaaa 1140
aacaatgtga gatgtctcca gcatttttac ggacccaatc atgagcactg ctttaataagg 1200
gtaagtcaca tcagttcccc acttataaac tgtgaggtat 1240

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&lt;210&gt; 186

&lt;211&gt; 413

&lt;212&gt; PRT

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&lt;213&gt; Homo Sapiens

&lt;400&gt; 186

```

Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
 1          5          10          15
Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys
 20          25          30
Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
 35          40          45
Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
 50          55          60
Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
 65          70          75          80
Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
 85          90          95
Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
100          105          110
Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
115          120          125
Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
130          135          140
Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys
145          150          155          160
Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val
165          170          175
Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe
180          185          190
Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp
195          200          205
His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp
210          215          220
Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu
225          230          235          240
Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn
245          250          255
Asn Phe Ile Tyr Phe Leu Thr Val Gln Arg Glu Thr Leu Asp Ala Gln
260          265          270
Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Ile Asn Ser Gly Leu
275          280          285
His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg
290          295          300
Lys Lys Arg Ser Thr Lys Lys Glu Val Leu Asn Ile Leu Gln Ala Ala
305          310          315          320
Tyr Val Ser Lys Pro Gly Ala Gln Leu Ala Arg Gln Ile Gly Ala Ser
325          330          335
Leu Asn Asp Asp Ile Leu Phe Gly Val Phe Ala Gln Ser Lys Pro Asp
340          345          350
Ser Ala Glu Pro Met Asp Arg Ser Ala Met Cys Ala Phe Pro Ile Lys
355          360          365
Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Asn Val Arg
370          375          380
Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg
385          390          395          400
Val Ser His Ile Ser Ser Pro Leu Ile Asn Cys Glu Val
405          410

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<210> 187  
 <211> 1405  
 <212> DNA  
 <213> Homo Sapiens

<400> 187  
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 tatcagcttc ccaacttcac cgcggaaca cccatccaga atgtcattct acatgagcat 180  
 cacattttcc ttggtgccac taactacatt tatgttttaa atgaggaaga ccttcagaag 240  
 gttgctgagt acaagactgg gcctgtgctg gaacacccag attgtttccc atgtcaggac 300  
 tgcagcagca aagccaattt atcaggaggt gtttggaaaa ataacatcaa catggctcta 360  
 gttgtcgaca cctactatga tgatcaactc attagctgtg gcagcgtcaa cagagggacc 420  
 tgcagcgaac atgtctttcc ccacaatcat actgctgaca tacagtcgga ggttcactgc 480  
 atattctccc cacagataga agagcccagc cagtgtcctg actgtgtggg gagcgccctg 540  
 ggagccaaag tcctttcatc tgtaaaggac cggttcatca acttctttgt aggcaatacc 600  
 ataaattctt cttattttcc agatcatcca ttgcattcga tatcagttag aaggctaaag 660  
 gaaacgaaag atggttttat gtttttgacg gaccagtcct acattgatgt tttacctgag 720  
 ttcagagatt cttaccccat taagtatgtc catgcctttg aaagcaacaa ttttatttac 780  
 ttcttgacgg tccaaaggga aactctagat gctcagactt ttcacacaag aataatcagg 840  
 ttctgttcca taaactctgg attgcattcc tacatggaaa tgcctctgga gtgtattctc 900  
 acagaaaaga gaaaaaagag atccacaaag aagggaagtgt ttaataactc tcaggctgcg 960  
 tatgtcagca agcctggggc ccagcttgct agacaaatag gagccagcct gaatgatgac 1020  
 attcttttctg ggggtgttcgc acaaagcaag ccagattctg ccgaaccaat ggatcgatct 1080  
 gccatgtgtg cattccctat caaatatgtc aacgacttct tcaacaagat cgtcaacaaa 1140  
 aacaatgtga gatgtctcca gcatttttac ggacccaatc atgagcactg ctttaataagg 1200  
 acacttctga gaaattcatc aggtgtgtaa gcgcgccgtg atgaatatcg aacagagttt 1260  
 accacagctt tgcagcgcgt tgacttatcc atgggtcaat tcagcgaagt cctcttaaca 1320  
 tctatatcca ccttcattaa aggagacctc accatagcta atcttgggac atcagagggt 1380  
 cgcttcatgc aggttaagtgc tttct 1405

<210> 188  
 <211> 468  
 <212> PRT  
 <213> Homo Sapiens

<400> 188  
 Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe  
 1 5 10 15  
 Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys  
 20 25 30  
 Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala  
 35 40 45  
 Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu  
 50 55 60  
 Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Asp Leu Gln Lys  
 65 70 75 80  
 Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe  
 85 90 95  
 Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp  
 100 105 110  
 Lys Asn Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp  
 115 120 125  
 Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His  
 130 135 140

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Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys  
 145 150 155 160  
 Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val  
 165 170 175  
 Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe  
 180 185 190  
 Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp  
 195 200 205  
 His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp  
 210 215 220  
 Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu  
 225 230 235 240  
 Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn  
 245 250 255  
 Asn Phe Ile Tyr Phe Leu Thr Val Gln Arg Glu Thr Leu Asp Ala Gln  
 260 265 270  
 Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Ile Asn Ser Gly Leu  
 275 280 285  
 His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg  
 290 295 300  
 Lys Lys Arg Ser Thr Lys Lys Glu Val Phe Asn Ile Leu Gln Ala Ala  
 305 310 315 320  
 Tyr Val Ser Lys Pro Gly Ala Gln Leu Ala Arg Gln Ile Gly Ala Ser  
 325 330 335  
 Leu Asn Asp Asp Ile Leu Phe Gly Val Phe Ala Gln Ser Lys Pro Asp  
 340 345 350  
 Ser Ala Glu Pro Met Asp Arg Ser Ala Met Cys Ala Phe Pro Ile Lys  
 355 360 365  
 Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Val Arg  
 370 375 380  
 Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg  
 385 390 395 400  
 Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr  
 405 410 415  
 Arg Thr Glu Phe Thr Thr Ala Leu Gln Arg Val Asp Leu Phe Met Gly  
 420 425 430  
 Gln Phe Ser Glu Val Leu Leu Thr Ser Ile Ser Thr Phe Ile Lys Gly  
 435 440 445  
 Asp Leu Thr Ile Ala Asn Leu Gly Thr Ser Glu Gly Arg Phe Met Gln  
 450 455 460  
 Val Ser Ala Phe  
 465

<210> 189  
 <211> 1557  
 <212> DNA  
 <213> Homo Sapiens

<400> 189  
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 tatcagcttc ccaacttcac cgcggaaaca cccatccaga atgtcattct acatgagcat 180  
 cacattttcc ttggtgccac taactacatt tatgttttaa atgaggaaga ccttcagaag 240  
 gttgctgagt acaagactgg gcctgtgctg gaacacccag attgtttccc atgtcaggac 300  
 tgcagcagca aagccaattt atcaggaggt gtttggaag ataacattaa catggctcta 360

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gttgctgaca cctactatga tgatcaactc attagctgtg gcagcgtcaa cagaggggacc 420
tgccagcgac atgtctttcc ccacaatcat actgctgaca tacagtcgga ggttcactgc 480
atattctccc cacagataga agagcccagc cagtgtcctg actgtgtggt gaggcgccctg 540
ggagccaaag tcctttcatc tgtaaaggac cggttcatca acttctttgt aggcaatacc 600
ataaattctt cttattttcc agatcatcca ttgcattcga tatcagttag aaggctaaag 660
gaaacgaaag atggttttat gtttttgacg gaccagtcct acattgatgt tttacctgag 720
ttcagagatt cttaccccat taagtattgt catgcctttg aaagcaacaa ttttattttac 780
ttcttgacgg tccaaaggga aactctagat gctcagactt ttcacacaag aataatcagg 840
ttctgttcca taaactctgg attgcattcc tacatggaaa tgcctctgga gtgtattctc 900
acagaaaaga gaaaaagag atccacaaag aagggaagtgt ttaataactc tcaggctgcg 960
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gacctgtgtg cattccctat caaatatgtc aacgacttct tcaacaagat cgtcaacaaa 1140
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tacacactgg ttatcactgg gaaggaggta agctgttccc acagggaatt tccatga 1557

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&lt;210&gt; 190

&lt;211&gt; 518

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 190

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Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
  1          5          10          15
Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys
  20          25          30
Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
  35          40          45
Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
  50          55          60
Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
  65          70          75          80
Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
  85          90          95
Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
  100          105          110
Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
  115          120          125
Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
  130          135          140
Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys
  145          150          155          160
Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val
  165          170          175
Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe
  180          185          190
Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp
  195          200          205
His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp
  210          215          220
Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu

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225					230					235				240
Phe	Arg	Asp	Ser	Tyr	Pro	Ile	Lys	Tyr	Val	His	Ala	Phe	Glu	Ser
				245					250					255
Asn	Phe	Ile	Tyr	Phe	Leu	Thr	Val	Gln	Arg	Glu	Thr	Leu	Asp	Ala
			260					265					270	
Thr	Phe	His	Thr	Arg	Ile	Ile	Arg	Phe	Cys	Ser	Ile	Asn	Ser	Gly
		275					280					285		
His	Ser	Tyr	Met	Glu	Met	Pro	Leu	Glu	Cys	Ile	Leu	Thr	Glu	Lys
	290					295					300			
Lys	Lys	Arg	Ser	Thr	Lys	Lys	Glu	Val	Phe	Asn	Ile	Leu	Gln	Ala
305					310					315				320
Tyr	Val	Ser	Lys	Pro	Gly	Ala	Gln	Leu	Ala	Arg	Gln	Ile	Gly	Ala
				325					330					335
Leu	Asn	Asp	Val	Ile	Leu	Phe	Gly	Val	Phe	Ala	Gln	Ser	Lys	Pro
		340					345						350	
Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser	Ala	Met	Cys	Ala	Phe	Pro	Ile
	355					360						365		
Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys	Ile	Val	Asn	Lys	Asn	Asn	Val
370						375				380				
Cys	Leu	Gln	His	Phe	Tyr	Gly	Pro	Asn	His	Glu	His	Cys	Phe	Asn
385					390					395				400
Thr	Leu	Leu	Arg	Asn	Ser	Ser	Gly	Cys	Glu	Ala	Arg	Arg	Asp	Glu
			405						410					415
Arg	Thr	Glu	Phe	Thr	Thr	Ala	Leu	Gln	Arg	Val	Asp	Leu	Phe	Met
		420						425					430	
Gln	Phe	Ser	Glu	Val	Leu	Leu	Thr	Ser	Ile	Ser	Thr	Phe	Ile	Lys
	435						440					445		
Asp	Leu	Thr	Ile	Ala	Asn	Leu	Gly	Thr	Ser	Glu	Gly	Arg	Phe	Met
	450					455				460				
Val	Val	Val	Ser	Arg	Ser	Gly	Pro	Ser	Thr	Pro	His	Val	Asn	Phe
465					470					475				480
Leu	Asp	Ser	His	Pro	Val	Ser	Pro	Glu	Val	Ile	Val	Glu	His	Thr
			485						490					495
Asn	Gln	Asn	Asp	Tyr	Thr	Leu	Val	Ile	Thr	Gly	Lys	Glu	Val	Ser
		500						505						510
Ser	His	Arg	Glu	Phe	Pro									
		515												

&lt;210&gt; 191

&lt;211&gt; 1789

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 191

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aggagcaatg gggagtgtaa agaggcacta gcaaagtccg agatgaatgt gaatatgaag 120
tatcagcttc ccaacttcac cgcggaaaca cccatccaga atgtcattct acatgagcat 180
cacattttcc ttggtgccac taactacatt tatgttttaa atgaggaaga ccttcagaag 240
gttgctgagt acaagactgg gcctgtgctg gaacaccagc attgtttccc atgtcaggac 300
tgcagcagca aagccaattt atcaggaggt gtttgaaaag ataacatcaa catggctcta 360
gttgctgaca cctactatga tgatcaactc attagctgtg gcagcgtcaa cagagggacc 420
tgccagcgac atgtctttcc ccacaatcat actgctgaca tacagtcgga ggttcactgc 480
atattctccc cacagataga agagcccagc cagtgtcctg actgtgtggt gagcgccctg 540
ggagccaaag tcctttcatc tgtaaaggac cggttcatca acttctttgt aggcaatacc 600
ataaattctt cttatttccc agatcatcca ttgcattcga tatcagttag aaggctaaag 660

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ttcttgacgg tccaaaggga aactctagat gctcagactt ttcacacaag aataatcagg 840
ttctgttcca taaactctgg attgcattcc tacatggaaa tgcctctgga gtgtattctc 900
acagaaaaga gaaaaaagag atccacaaag aagggaagtgt ttaataact ttaggctgag 960
tatgtcagca agcctggggc ccagcttgct agacaaatag gagccagccc gaatgatgac 1020
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gccatgtgtg cattccctat caaatatgtc aacgacttct tcaacaagat cgtcaacaaa 1140
aacaatgtga gatgtctcca gcattttttac ggacccaatc atgagcactg ctttaataagg 1200
acacttctga gaaattcatc aggtgtgaa gcgcgccgtg atgaatatcg aacagagttt 1260
accacagctt tgcagcgcgt tgaacttattc atgggtcaat tcagcgaagt cctcttaaca 1320
tctatatcca ccttcattaa aggagacctc accatagcta atcttgggac atcagagggt 1380
cgcttcagtc aggttgtggg ttctcgatca ggaccatcaa cccctcatgt gaattttctc 1440
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tgccacgaca aatgtgtgag atcggaggaa tgcttgagcg ggacatggac tcaacagatc 1680
tgtctgcctg caatctacaa ggtaggaatc tctaacagct ggcatacatg tttttgtttg 1740
gtgttttttt tttttttttg gtttggtttg gtttggtttt tgtttttttt 1789

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&lt;210&gt; 192

&lt;211&gt; 596

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 192

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Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
  1           5           10           15
Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys
      20           25           30
Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
      35           40           45
Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
      50           55           60
Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
      65           70           75           80
Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
      85           90           95
Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
      100          105          110
Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
      115          120          125
Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
      130          135          140
Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys
      145          150          155          160
Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val
      165          170          175
Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe
      180          185          190
Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp
      195          200          205
His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp
      210          215          220
Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu
      225          230          235          240

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Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn
      245      250      255
Asn Phe Ile Tyr Phe Leu Thr Val Gln Arg Glu Thr Leu Asp Ala Gln
      260      265      270
Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Ile Asn Ser Gly Leu
      275      280      285
His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg
      290      295      300
Lys Lys Arg Ser Thr Lys Lys Glu Val Phe Asn Ile Leu Gln Ala Ala
305      310      315      320
Tyr Val Ser Lys Pro Gly Ala Gln Leu Ala Arg Gln Ile Gly Ala Ser
      325      330      335
Pro Asn Asp Asp Ile Leu Phe Gly Val Phe Ala Gln Ser Lys Pro Asp
      340      345      350
Ser Ala Glu Pro Met Asp Arg Ser Ala Met Cys Ala Phe Pro Ile Lys
      355      360      365
Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Val Arg
      370      375      380
Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg
385      390      395      400
Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr
      405      410      415
Arg Thr Glu Phe Thr Thr Ala Leu Gln Arg Val Asp Leu Phe Met Gly
      420      425      430
Gln Phe Ser Glu Val Leu Leu Thr Ser Ile Ser Thr Phe Ile Lys Gly
      435      440      445
Asp Leu Thr Ile Ala Asn Leu Gly Thr Ser Glu Gly Arg Phe Met Gln
      450      455      460
Val Val Val Ser Arg Ser Gly Pro Ser Thr Pro His Val Asn Phe Leu
465      470      475      480
Leu Asp Ser His Pro Val Ser Pro Glu Val Ile Val Glu His Thr Leu
      485      490      495
Asn Gln Asn Gly Tyr Thr Leu Val Ile Thr Gly Lys Lys Ile Thr Lys
      500      505      510
Ile Pro Leu Asn Gly Leu Gly Cys Arg His Phe Gln Ser Cys Ser Gln
      515      520      525
Cys Leu Ser Ala Pro Pro Phe Val Gln Cys Gly Trp Cys His Asp Lys
      530      535      540
Cys Val Arg Ser Glu Glu Cys Leu Ser Gly Thr Trp Thr Gln Gln Ile
545      550      555      560
Cys Leu Pro Ala Ile Tyr Lys Val Gly Ile Ser Asn Ser Trp His Thr
      565      570      575
Cys Phe Cys Leu Val Phe Phe Phe Phe Trp Phe Gly Leu Val Cys
      580      585      590
Phe Leu Phe Phe
      595

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&lt;210&gt; 193

&lt;211&gt; 1936

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 193

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atgaaggccc ccgctgtgct tgcacctggc atcctcgtgc tcctgtttac cttgggtgcag 60
aggagcaatg gggagtgtaa agaggcacta gcaaagtccg agatgaatgt gaatatgaag 120

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tatcggttcc ccaacttcac cgcggaaaca cccatccaga atgtcattct acatgagcat 180
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gttgctgagt acaagactgg gcctgtgctg gaacacccag attgtttccc atgtcaggac 300
tgcagcagca aagccaattt atcaggagggt gtttggagag ataacatcaa catggctcta 360
gttgtegaca cctactatga tgatcaactc attagctgtg gcagcgtcaa cagagggacc 420
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atattctccc cacagataga agatcccagc cagtgtcctg actgtgtggt gagcgccctg 540
ggagccaaag tcctttcatc tgtaaaggac cggttcatca acttctttgt aggcaatacc 600
ataaattcct cttattttcc agatcatcca ttgcattcga tatcattgag aaggctaaag 660
gaaacgaaag atggttttat gtttttgacg gaccagtcct acattgatgt tttacctgag 720
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acagagaaga gaaaaaagag atccacaaag aagggaagtgt ttaataact ttaggctgag 960
tatgtcagca agcctggggc ccagcttgct agacaaatag gagccagcct gaatgatgac 1020
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tggtcagtg ggctgggtgcc acaacaaatg tgtgcgatcg gaggaatgcc tgagcggggac 1740
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&lt;210&gt; 194

&lt;211&gt; 408

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 194

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Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
 1           5           10           15
Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys
          20          25          30
Ser Glu Met Asn Val Asn Met Lys Tyr Arg Leu Pro Asn Phe Thr Ala
          35          40          45
Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
          50          55          60
Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
          65          70          75          80
Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
          85          90          95
Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
          100         105         110
Arg Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
          115         120         125
Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
          130         135         140

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Ala	Phe	Pro	His	Asn	His	Thr	Ala	Asp	Ile	Gln	Ser	Glu	Val	His	Cys
145					150					155					160
Ile	Phe	Ser	Pro	Gln	Ile	Glu	Asp	Pro	Ser	Gln	Cys	Pro	Asp	Cys	Val
				165					170					175	
Val	Ser	Ala	Leu	Gly	Ala	Lys	Val	Leu	Ser	Ser	Val	Lys	Asp	Arg	Phe
			180					185					190		
Ile	Asn	Phe	Phe	Val	Gly	Asn	Thr	Ile	Asn	Ser	Ser	Tyr	Phe	Pro	Asp
		195					200					205			
His	Pro	Leu	His	Ser	Ile	Ser	Leu	Arg	Arg	Leu	Lys	Glu	Thr	Lys	Asp
	210					215					220				
Gly	Phe	Met	Phe	Leu	Thr	Asp	Gln	Ser	Tyr	Ile	Asp	Val	Leu	Pro	Glu
225					230					235					240
Phe	Arg	Asp	Ser	Tyr	Pro	Ile	Lys	Tyr	Val	His	Ala	Phe	Glu	Ser	Asn
				245					250					255	
Asn	Phe	Ile	Tyr	Phe	Leu	Thr	Val	Gln	Arg	Glu	Thr	Leu	Asp	Ala	Gln
			260					265					270		
Thr	Phe	His	Ala	Arg	Ile	Ile	Arg	Phe	Cys	Ser	Ile	Asn	Ser	Gly	Leu
		275					280					285			
His	Ser	Tyr	Met	Glu	Met	Pro	Leu	Glu	Cys	Ile	Leu	Thr	Glu	Lys	Arg
	290					295					300				
Lys	Lys	Arg	Ser	Thr	Lys	Lys	Glu	Val	Phe	Asn	Ile	Leu	Gln	Ala	Ala
305					310					315					320
Tyr	Val	Ser	Lys	Pro	Gly	Ala	Gln	Leu	Ala	Arg	Gln	Ile	Gly	Ala	Ser
				325					330					335	
Leu	Asn	Asp	Asp	Ile	Leu	Phe	Gly	Val	Phe	Ala	Gln	Ser	Lys	Pro	Asp
			340					345					350		
Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser	Ala	Met	Cys	Ala	Phe	Pro	Ile	Lys
		355					360					365			
Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys	Ile	Val	Asn	Lys	Asn	Asn	Val	Arg
	370					375					380				
Cys	Leu	Gln	His	Phe	Tyr	Gly	Pro	Asn	His	Glu	His	Cys	Phe	Asn	Arg
385					390					395					400
Ala	Glu	Asn	Val	Leu	Asp	Trp	Arg								
				405											

&lt;210&gt; 195

&lt;211&gt; 1888

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 195

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atgaaggccc ccgctgtgct tgcacctggc atcctcgtgc tcctgtttac cttggtgcag 60
aggagcaatg gggagtgtaa agaggcacta gcaaagtccg agatgaatgt gaatatgaag 120
tatcagcttc ccaacttcac cgcggaaaca cccatccaga atgtcattct acatgagcat 180
cacattttcc ttggtgccac taactacatt tatgttttaa atgaggaaga ctttcagaag 240
gttgctgagt acaagactgg gcctgtgctg gaacacccag attgtttccc atgtcaggac 300
tgcagcagca aagccaattt atcaggaggt gtttggaaag ataacatcaa catggctcta 360
gttgctcgaca cctactatga tgatcaactc attagctgtg gcagcgtcaa cagagggacc 420
tgccagcgac atgtctttcc ccacaatcat actgctgaca tacagtcgga ggctcactgc 480
atattctccc cacagataga agagcccagt cagtgtcctg actgtgtggt gagcgccctg 540
ggagccaaaag tcctttcatc tgtaaaaggac cggttcatca acttctttgt aggcaatacc 600
ataaattcct cttatttccc agatcatcca ttgcattcga tatcagttag aaggctaaag 660
gaaacgaaaag atgggtttat gtttttgacg gaccagtcct acattgatgt ttacctgag 720
ttcagagatt cttaccccat taagtatgtc catgcctttg aaagcaacaa ttttatttac 780
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tatgtcagca agcctggggc ccagcttgct agacaaatag gagccagcct gaatgatgac 1020
attcttttcg ggggtgttcg acaaaagcaag ccagattctg ccgaaccaat ggatcgatct 1080
gccatgtgtg cattccctat caaatatgtc aacgacttct tcaacaagat cgtcaacaaa 1140
aacaatgtga gatgtctcca gcatttttac ggacccaatc atgagcactg ctttaaatagg 1200
acacttctga gaaattcatc aggctgtgaa gcgcgccgtg atgaatatcg aacagagttt 1260
accacagctt tgcagcgcgt tgacttattc atgggtcaat tcagcgaagt cctcttaaca 1320
tctatatcca ccttcattaa aggagacctc accatagcta atcttgggac atcagagggg 1380
cgcttcatgc aggttgtggt ttctcgatca ggaccatcaa cccctcatgt gaattttctc 1440
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tacacactgg ttatcactgg gaagaagatc acgaagatcc cattgaatgg cttgggctgc 1560
agacatttcc agtcctgcag tcaatgcctc tctgcccac cctttgttca gtgtggctgg 1620
tgccacgaca aatgtgtgcg atcggaggaa tgcctgagcg ggacatggac tcaacagatc 1680
tgtctgcctg caatctacaa ggttttccca aatagtgcac cccttgaagg agggacaagg 1740
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actagagttc tccttggaat tgagagctgc accttgactt taagtgagag cacgatgaat 1860
acgtaaggat cttaaaatgc ttgtgctg 1888

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&lt;210&gt; 196

&lt;211&gt; 621

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 196

```

Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
 1          5          10          15
Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys
          20          25          30
Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
          35          40          45
Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
          50          55          60
Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
          65          70          75          80
Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
          85          90          95
Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
          100          105          110
Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
          115          120          125
Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
          130          135          140
Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Ala His Cys
          145          150          155          160
Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val
          165          170          175
Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe
          180          185          190
Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp
          195          200          205
His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp
          210          215          220
Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu
          225          230          235          240
Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn

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				245					250					255	
Asn	Phe	Ile	Tyr	Phe	Leu	Thr	Val	Gln	Arg	Glu	Thr	Leu	Asp	Ala	Gln
			260					265					270		
Thr	Phe	His	Thr	Arg	Ile	Ile	Arg	Phe	Cys	Ser	Ile	Asn	Ser	Gly	Leu
			275					280					285		
His	Ser	Tyr	Met	Glu	Met	Pro	Leu	Glu	Cys	Ile	Leu	Thr	Glu	Lys	Arg
			290				295					300			
Lys	Lys	Arg	Ser	Thr	Lys	Lys	Glu	Val	Phe	Asn	Ile	Leu	Gln	Ala	Ala
305					310					315					320
Tyr	Val	Ser	Lys	Pro	Gly	Ala	Gln	Leu	Ala	Arg	Gln	Ile	Gly	Ala	Ser
				325					330					335	
Leu	Asn	Asp	Asp	Ile	Leu	Phe	Gly	Val	Phe	Ala	Gln	Ser	Lys	Pro	Asp
			340					345					350		
Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser	Ala	Met	Cys	Ala	Phe	Pro	Ile	Lys
			355				360						365		
Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys	Ile	Val	Asn	Lys	Asn	Asn	Val	Arg
			370				375					380			
Cys	Leu	Gln	His	Phe	Tyr	Gly	Pro	Asn	His	Glu	His	Cys	Phe	Asn	Arg
385					390					395					400
Thr	Leu	Leu	Arg	Asn	Ser	Ser	Gly	Cys	Glu	Ala	Arg	Arg	Asp	Glu	Tyr
				405					410					415	
Arg	Thr	Glu	Phe	Thr	Thr	Ala	Leu	Gln	Arg	Val	Asp	Leu	Phe	Met	Gly
			420					425					430		
Gln	Phe	Ser	Glu	Val	Leu	Leu	Thr	Ser	Ile	Ser	Thr	Phe	Ile	Lys	Gly
			435				440					445			
Asp	Leu	Thr	Ile	Ala	Asn	Leu	Gly	Thr	Ser	Glu	Gly	Arg	Phe	Met	Gln
			450			455					460				
Val	Val	Val	Ser	Arg	Ser	Gly	Pro	Ser	Thr	Pro	His	Val	Asn	Phe	Leu
465					470					475					480
Leu	Asp	Ser	His	Pro	Val	Ser	Pro	Glu	Val	Ile	Val	Glu	His	Thr	Leu
				485					490					495	
Asn	Gln	Asn	Gly	Tyr	Thr	Leu	Val	Ile	Thr	Gly	Lys	Lys	Ile	Thr	Lys
			500					505					510		
Ile	Pro	Leu	Asn	Gly	Leu	Gly	Cys	Arg	His	Phe	Gln	Ser	Cys	Ser	Gln
			515				520					525			
Cys	Leu	Ser	Ala	Pro	Pro	Phe	Val	Gln	Cys	Gly	Trp	Cys	His	Asp	Lys
			530			535					540				
Cys	Val	Arg	Ser	Glu	Glu	Cys	Leu	Ser	Gly	Thr	Trp	Thr	Gln	Gln	Ile
545					550					555					560
Cys	Leu	Pro	Ala	Ile	Tyr	Lys	Val	Phe	Pro	Asn	Ser	Ala	Pro	Leu	Glu
				565					570					575	
Gly	Gly	Thr	Arg	Leu	Thr	Ile	Cys	Gly	Trp	Asp	Phe	Gly	Phe	Arg	Arg
			580					585					590		
Asn	Asn	Lys	Phe	Asp	Leu	Lys	Lys	Thr	Arg	Val	Leu	Leu	Gly	Asn	Glu
			595												

<400> 197  
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cacattttcc ttggtgccac taactacatt tatgttttaa atgaggaaga ccttcagaag 240
gttgctgagt acaagactgg gcctgtgctg gaacacccag attgtttccc atgtcaggac 300
tgagcagca aagccaattt atcaggaggt gtttggaag ataacatcaa catggctcta 360
gttgctgaca cctactatga tgatcaactc attagctgtg gcagcgtcaa cagagggacc 420
tgccagcgac atgtctttcc ccacaatcat actgctgaca tacagtcgga gggtcactgc 480
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ataaattctt cttattttcc agatcatcca ttgcatcga tatcagttag aaggctaaag 660
gaaacgaaag atggttttat gtttttgacg gaccagtcct acattgatgt tttacctgag 720
ttcagagatt cttaccccat taagtatgtc catgcctttg aaagcaacaa ttttatttac 780
ttcttgacgg tccaaagggg aactctagat gctcagactt ttcacacaag aataatcagg 840
ttctgttcca taaactctgg attgcattcc tacatggaaa tgcctctgga gtgtattctc 900
acagaaaaga gaaaaaagag atccacaaag aagggaagtgt ttaataactc tcaggctgcg 960
tatgtcagca agcctggggc ccagcttgct agacaaatag gagccagcct gaatgatgac 1020
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tacacactgg ttatcactgg gaagaagatc acgaagatcc cattgaatgg cttgggctgc 1560
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ctgaccatat gtggctggga ctttggattt cggagggaata ataaatttga tttaaagaaa 1800
actagagttc tccttggaag tgagagctgc accttgactt taagttagag cagcatgaat 1860
acattgaaat gcacagtgg tcctgccatg aataagcatt tcaatatgtc cataattatt 1920
tcaaatggcc acgggacaac acaatacagt acattctcct atgtggtaag gaagattcta 1980
tcctatcatg ttgga                                     1995

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&lt;210&gt; 198

&lt;211&gt; 664

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 198

```

Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
  1           5           10           15
Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys
      20           25           30
Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
      35           40           45
Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
      50           55           60
Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
      65           70           75           80
Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
      85           90           95
Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
      100          105          110
Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
      115          120          125

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Gln	Leu	Ile	Ser	Cys	Gly	Ser	Val	Asn	Arg	Gly	Thr	Cys	Gln	Arg	His
130						135					140				
Val	Phe	Pro	His	Asn	His	Thr	Ala	Asp	Ile	Gln	Ser	Glu	Val	His	Cys
145				150						155					160
Ile	Phe	Ser	Pro	Gln	Ile	Glu	Glu	Pro	Ser	Gln	Cys	Pro	Asp	Cys	Val
				165					170					175	
Val	Ser	Ala	Leu	Gly	Ala	Lys	Val	Leu	Ser	Ser	Val	Lys	Asp	Arg	Phe
			180					185					190		
Ile	Asn	Phe	Phe	Val	Gly	Asn	Thr	Ile	Asn	Ser	Ser	Tyr	Phe	Pro	Asp
		195					200					205			
His	Pro	Leu	His	Ser	Ile	Ser	Val	Arg	Arg	Leu	Lys	Glu	Thr	Lys	Asp
210						215					220				
Gly	Phe	Met	Phe	Leu	Thr	Asp	Gln	Ser	Tyr	Ile	Asp	Val	Leu	Pro	Glu
225				230						235					240
Phe	Arg	Asp	Ser	Tyr	Pro	Ile	Lys	Tyr	Val	His	Ala	Phe	Glu	Ser	Asn
				245					250					255	
Asn	Phe	Ile	Tyr	Phe	Leu	Thr	Val	Gln	Arg	Glu	Thr	Leu	Asp	Ala	Gln
		260						265					270		
Thr	Phe	His	Thr	Arg	Ile	Ile	Arg	Phe	Cys	Ser	Ile	Asn	Ser	Gly	Leu
		275					280					285			
His	Ser	Tyr	Met	Glu	Met	Pro	Leu	Glu	Cys	Ile	Leu	Thr	Glu	Lys	Arg
290						295					300				
Lys	Lys	Arg	Ser	Thr	Lys	Lys	Glu	Val	Phe	Asn	Ile	Leu	Gln	Ala	Ala
305				310						315					320
Tyr	Val	Ser	Lys	Pro	Gly	Ala	Gln	Leu	Ala	Arg	Gln	Ile	Gly	Ala	Ser
				325					330					335	
Leu	Asn	Asp	Asp	Ile	Leu	Phe	Gly	Val	Phe	Ala	Gln	Ser	Lys	Pro	Asp
		340						345					350		
Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser	Ala	Met	Cys	Ala	Phe	Pro	Ile	Lys
		355					360					365			
Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys	Ile	Val	Asn	Lys	Asn	Asn	Val	Arg
370						375					380				
Cys	Leu	Gln	His	Phe	Tyr	Gly	Pro	Asn	His	Glu	His	Cys	Phe	Asn	Arg
385				390						395					400
Thr	Leu	Leu	Arg	Asn	Ser	Ser	Gly	Cys	Glu	Ala	Arg	Arg	Asp	Glu	Tyr
				405					410					415	
Arg	Thr	Glu	Phe	Thr	Thr	Ala	Leu	Gln	Arg	Val	Asp	Leu	Phe	Met	Gly
			420					425					430		
Gln	Phe	Ser	Glu	Val	Leu	Leu	Thr	Ser	Ile	Ser	Thr	Phe	Ile	Lys	Gly
		435					440					445			
Asp	Leu	Thr	Ile	Ala	Asn	Leu	Gly	Thr	Ser	Glu	Gly	Arg	Phe	Met	Gln
450						455					460				
Val	Val	Val	Ser	Arg	Ser	Gly	Pro	Ser	Thr	Pro	His	Val	Asn	Phe	Leu
465					470					475					480
Met	Asp	Ser	His	Pro	Val	Ser	Pro	Glu	Val	Ile	Val	Glu	His	Thr	Leu
				485				490						495	
Asn	Gln	Asn	Gly	Tyr	Thr	Leu	Val	Ile	Thr	Gly	Lys	Lys	Ile	Thr	Lys
		500						505					510		
Ile	Pro	Leu	Asn	Gly	Leu	Gly	Cys	Arg	His	Phe	Gln	Ser	Cys	Ser	Gln
		515					520					525			
Cys	Leu	Ser	Ala	Pro	Pro	Phe	Val	Gln	Cys	Gly	Trp	Cys	His	Asp	Lys
530						535					540				
Cys	Val	Arg	Ser	Glu	Glu	Cys	Leu	Ser	Gly	Thr	Trp	Thr	Gln	Gln	Ile
545				550						555					560
Cys	Leu	Pro	Ala	Ile	Tyr	Lys	Val	Phe	Pro	Asn	Ser	Ala	Pro	Leu	Glu
				565					570					575	

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Gly	Gly	Thr	Arg	Leu	Thr	Ile	Cys	Gly	Trp	Asp	Phe	Gly	Phe	Arg	Arg
			580					585				590			
Asn	Asn	Lys	Phe	Asp	Leu	Lys	Lys	Thr	Arg	Val	Leu	Leu	Gly	Asn	Glu
		595					600				605				
Ser	Cys	Thr	Leu	Thr	Leu	Ser	Glu	Ser	Thr	Met	Asn	Thr	Leu	Lys	Cys
	610					615				620					
Thr	Val	Gly	Pro	Ala	Met	Asn	Lys	His	Phe	Asn	Met	Ser	Ile	Ile	Ile
625					630					635					640
Ser	Asn	Gly	His	Gly	Thr	Thr	Gln	Tyr	Ser	Thr	Phe	Ser	Tyr	Val	Val
			645						650					655	
Arg	Lys	Ile	Leu	Ser	Tyr	His	Val								
			660												

&lt;210&gt; 199

&lt;211&gt; 2170

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 199

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cacattttcc ttgggtgccac taactacatt tatgttttaa atgaggaaga ccttcagaag 240
gttgctgagt acaagactgg gcctgtgctg gaacaccagc attgtttccc atgtcaggac 300
tgcagcagca aagccaattt atcaggaggt gtttggaaag ataacatcaa catggctcta 360
gttgctcgaca cctactatga tgatcaactc attagctgtg gcagcgtcaa cagagggacc 420
tgccacgac atgtctttcc ccacaatcat cctgctgaca tacagtcgga gggttactgc 480
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ataaattctt cttatttccc agatcatcca ttgcattcga tatcagttag aaggctaaaag 660
gaaacgaaaag atggttttat gtttttgacg gaccagtcct acattgatgt tttacctgag 720
ttcagagatt cttaccccat taagtatgtc catgcctttg aaagcaacaa ttttatattac 780
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tatgttagca agcctggggc ccagcttgct agacaaatag gagccagcct gaatgatgac 1020
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- 151 -

aaattaagca

2170

&lt;210&gt; 200

&lt;211&gt; 719

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 200

Met	Lys	Ala	Pro	Ala	Val	Leu	Ala	Pro	Gly	Ile	Leu	Val	Leu	Leu	Phe
1				5					10				15		
Thr	Leu	Val	Gln	Arg	Ser	Asn	Gly	Glu	Cys	Lys	Glu	Ala	Leu	Ala	Lys
			20					25					30		
Ser	Glu	Met	Asn	Val	Asn	Met	Lys	Tyr	Gln	Leu	Pro	Asn	Phe	Thr	Ala
		35					40					45			
Glu	Thr	Pro	Ile	Gln	Asn	Val	Ile	Leu	His	Glu	His	His	Ile	Phe	Leu
		50				55				60					
Gly	Ala	Thr	Asn	Tyr	Ile	Tyr	Val	Leu	Asn	Glu	Glu	Asp	Leu	Gln	Lys
65					70					75				80	
Val	Ala	Glu	Tyr	Lys	Thr	Gly	Pro	Val	Leu	Glu	His	Pro	Asp	Cys	Phe
				85					90					95	
Pro	Cys	Gln	Asp	Cys	Ser	Ser	Lys	Ala	Asn	Leu	Ser	Gly	Gly	Val	Trp
			100					105					110		
Lys	Asp	Asn	Ile	Asn	Met	Ala	Leu	Val	Val	Asp	Thr	Tyr	Tyr	Asp	Asp
		115					120					125			
Gln	Leu	Ile	Ser	Cys	Gly	Ser	Val	Asn	Arg	Gly	Thr	Cys	Gln	Arg	His
		130				135					140				
Val	Phe	Pro	His	Asn	His	Pro	Ala	Asp	Ile	Gln	Ser	Glu	Val	His	Cys
145					150					155					160
Ile	Phe	Ser	Pro	Gln	Ile	Glu	Glu	Pro	Ser	Gln	Cys	Pro	Asp	Cys	Val
				165					170					175	
Val	Ser	Ala	Leu	Gly	Ala	Lys	Val	Leu	Ser	Ser	Val	Lys	Asp	Arg	Phe
			180					185					190		
Ile	Asn	Phe	Phe	Val	Gly	Asn	Thr	Ile	Asn	Ser	Ser	Tyr	Phe	Pro	Asp
		195					200					205			
His	Pro	Leu	His	Ser	Ile	Ser	Val	Arg	Arg	Leu	Lys	Glu	Thr	Lys	Asp
		210				215					220				
Gly	Phe	Met	Phe	Leu	Thr	Asp	Gln	Ser	Tyr	Ile	Asp	Val	Leu	Pro	Glu
225					230					235				240	
Phe	Arg	Asp	Ser	Tyr	Pro	Ile	Lys	Tyr	Val	His	Ala	Phe	Glu	Ser	Asn
				245					250					255	
Asn	Phe	Ile	Tyr	Phe	Leu	Thr	Val	Gln	Arg	Glu	Thr	Leu	Asp	Ala	Gln
			260					265					270		
Thr	Phe	His	Thr	Arg	Ile	Ile	Arg	Phe	Cys	Ser	Ile	Asn	Ser	Gly	Leu
		275					280					285			
His	Ser	Tyr	Met	Glu	Met	Pro	Leu	Glu	Cys	Ile	Leu	Thr	Glu	Lys	Arg
		290				295					300				
Lys	Lys	Arg	Ser	Thr	Lys	Lys	Glu	Val	Phe	Asn	Ile	Leu	Gln	Ala	Ala
305					310					315				320	
Tyr	Val	Ser	Lys	Pro	Gly	Ala	Gln	Leu	Ala	Arg	Gln	Ile	Gly	Ala	Ser
				325					330					335	
Leu	Asn	Asp	Asp	Ile	Leu	Phe	Gly	Val	Phe	Ala	Gln	Ser	Lys	Pro	Asp
				340				345					350		
Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser	Ala	Met	Cys	Ala	Phe	Pro	Ile	Lys
		355					360					365			
Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys	Ile	Val	Asn	Lys	Asn	Asn	Val	Arg
		370				375					380				

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Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg  
 385 390 395 400  
 Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr  
 405 410 415  
 Arg Thr Glu Phe Thr Thr Ala Leu Gln Arg Val Asp Leu Phe Met Gly  
 420 425 430  
 Gln Phe Ser Glu Val Leu Leu Thr Ser Ile Ser Thr Phe Ile Lys Gly  
 435 440 445  
 Asp Leu Thr Ile Ala Asn Leu Gly Thr Ser Glu Gly Arg Phe Met Gln  
 450 455 460  
 Val Val Val Ser Arg Ser Gly Pro Ser Thr Pro His Val Asn Phe Leu  
 465 470 475 480  
 Leu Asp Ser His Pro Val Ser Pro Glu Val Ile Val Glu His Thr Leu  
 485 490 495  
 Asn Gln Asn Gly His Thr Leu Val Ile Thr Gly Lys Lys Ile Thr Lys  
 500 505 510  
 Ile Pro Leu Asn Gly Leu Gly Cys Arg His Phe Gln Ser Cys Ser Gln  
 515 520 525  
 Cys Leu Ser Ala Pro Pro Phe Val Gln Cys Gly Trp Cys His Asp Lys  
 530 535 540  
 Cys Val Arg Ser Glu Glu Cys Leu Ser Gly Thr Trp Thr Gln Gln Ile  
 545 550 555 560  
 Cys Leu Pro Ala Ile Tyr Lys Val Phe Pro Asn Ser Ala Pro Leu Glu  
 565 570 575  
 Gly Gly Thr Arg Leu Thr Ile Cys Gly Trp Asp Phe Gly Phe Arg Arg  
 580 585 590  
 Asn Asn Lys Phe Asp Leu Lys Lys Thr Arg Val Leu Leu Gly Asn Glu  
 595 600 605  
 Ser Cys Thr Leu Thr Leu Ser Glu Ser Thr Met Asn Thr Leu Lys Cys  
 610 615 620  
 Thr Val Gly Pro Ala Met Asn Lys His Phe Asn Met Ser Ile Ile Ile  
 625 630 635 640  
 Ser Asn Gly His Gly Thr Thr Gln Tyr Ser Thr Phe Ser Tyr Val Asp  
 645 650 655  
 Pro Val Ile Thr Ser Ile Ser Pro Lys Tyr Gly Pro Met Ala Gly Gly  
 660 665 670  
 Thr Leu Leu Thr Leu Thr Gly Asn Tyr Leu Asn Ser Gly Asn Ser Arg  
 675 680 685  
 His Ile Ser Ile Gly Gly Lys Thr Cys Thr Leu Lys Arg Cys Cys Lys  
 690 695 700  
 Phe Ile Phe Cys Cys Ile Cys Gln Phe Glu Leu Ile Ser Val Pro  
 705 710 715

&lt;210&gt; 201

&lt;211&gt; 2194

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 201

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&lt;210&gt; 202

&lt;211&gt; 697

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 202

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Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
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Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys
           20           25           30
Ser Glu Met Asn Ala Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
           35           40           45
Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
           50           55           60
Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
           65           70           75           80
Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
           85           90           95
Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
           100          105          110
Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
           115          120          125
Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
           130          135          140

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Val	Phe	Pro	His	Asn	His	Thr	Ala	Asp	Ile	Gln	Ser	Glu	Val	His	Cys
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Ile	Phe	Ser	Pro	Gln	Ile	Glu	Glu	Pro	Ser	Gln	Cys	Pro	Asp	Cys	Val
				165					170						175
Val	Ser	Ala	Leu	Gly	Ala	Lys	Val	Leu	Ser	Ser	Val	Lys	Asp	Arg	Phe
			180					185					190		
Ile	Asn	Phe	Phe	Val	Gly	Asn	Thr	Ile	Asn	Ser	Ser	Tyr	Phe	Pro	Asp
		195					200					205			
His	Pro	Leu	His	Ser	Ile	Ser	Val	Arg	Arg	Leu	Lys	Glu	Thr	Lys	Asp
	210				215						220				
Gly	Phe	Met	Phe	Leu	Thr	Asp	Gln	Ser	Tyr	Ile	Asp	Val	Leu	Pro	Glu
225					230					235					240
Phe	Arg	Asp	Ser	Tyr	Pro	Ile	Lys	Tyr	Val	His	Ala	Phe	Glu	Ser	Asn
				245					250						255
Asn	Phe	Ile	Tyr	Phe	Leu	Thr	Val	Gln	Arg	Glu	Thr	Leu	Asp	Ala	Gln
			260					265					270		
Thr	Phe	His	Thr	Arg	Ile	Ile	Arg	Phe	Cys	Ser	Ile	Asn	Ser	Gly	Leu
		275					280					285			
His	Ser	Tyr	Met	Glu	Met	Pro	Leu	Glu	Cys	Ile	Leu	Thr	Glu	Lys	Arg
	290					295					300				
Lys	Lys	Arg	Ser	Thr	Lys	Lys	Glu	Val	Phe	Asn	Ile	Leu	Gln	Ala	Ala
305					310					315					320
Tyr	Val	Ser	Lys	Pro	Gly	Ala	Gln	Leu	Ala	Arg	Gln	Ile	Gly	Ala	Ser
				325					330						335
Leu	Asn	Asp	Asp	Ile	Leu	Phe	Gly	Val	Phe	Ala	Gln	Ser	Lys	Pro	Asp
			340					345					350		
Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser	Ala	Met	Cys	Ala	Phe	Pro	Ile	Lys
		355					360					365			
Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys	Ile	Val	Asn	Lys	Asn	Asn	Val	Arg
	370					375					380				
Cys	Leu	Gln	His	Phe	Tyr	Gly	Pro	Asn	His	Glu	His	Cys	Phe	Asn	Arg
385					390					395					400
Thr	Leu	Leu	Arg	Asn	Ser	Ser	Gly	Cys	Glu	Ala	Arg	Arg	Asp	Glu	Tyr
				405					410					415	
Arg	Thr	Glu	Phe	Thr	Thr	Ala	Leu	Gln	Arg	Val	Asp	Leu	Phe	Met	Gly
			420					425					430		
Gln	Phe	Ser	Glu	Val	Leu	Leu	Thr	Ser	Ile	Ser	Thr	Phe	Ile	Lys	Gly
			435				440					445			
Asp	Leu	Thr	Ile	Ala	Asn	Leu	Gly	Thr	Ser	Glu	Gly	Arg	Phe	Met	Gln
	450					455					460				
Val	Val	Val	Ser	Arg	Ser	Gly	Pro	Ser	Thr	Pro	His	Val	Asn	Phe	Leu
465					470					475					480
Leu	Asp	Ser	His	Pro	Val	Ser	Pro	Glu	Val	Ile	Val	Glu	His	Thr	Leu
				485					490					495	
Asn	Gln	Asn	Gly	Tyr	Thr	Leu	Val	Ile	Thr	Gly	Lys	Lys	Ile	Thr	Lys
			500					505					510		
Thr	Pro	Leu	Asn	Gly	Leu	Gly	Cys	Arg	His	Phe	Gln	Ser	Cys	Ser	Gln
		515					520					525			
Cys	Leu	Ser	Ala	Pro	Pro	Phe	Val	Gln	Cys	Gly	Trp	Cys	His	Asp	Lys
	530					535					540				
Cys	Val	Arg	Ser	Glu	Glu	Cys	Leu	Ser	Gly	Thr	Trp	Thr	Gln	Gln	Ile
545					550					555					560
Cys	Leu	Pro	Ala	Ile	Tyr	Lys	Val	Phe	Pro	Asn	Ser	Ala	Pro	Leu	Glu
				565					570					575	
Gly	Gly	Thr	Arg	Leu	Thr	Ile	Cys	Gly	Trp	Asp	Phe	Gly	Phe	Arg	Arg
			580					585					590		

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Asn	Asn	Lys	Phe	Asp	Leu	Lys	Lys	Thr	Arg	Val	Leu	Leu	Gly	Asn	Glu
	595					600					605				
Ser	Cys	Thr	Leu	Thr	Leu	Ser	Glu	Ser	Thr	Met	Asn	Thr	Leu	Lys	Cys
610						615					620				
Thr	Val	Gly	Pro	Ala	Met	Asn	Lys	His	Phe	Asn	Met	Ser	Ile	Ile	Ile
625					630					635					640
Ser	Asn	Gly	His	Gly	Thr	Thr	Gln	Tyr	Ser	Thr	Phe	Ser	Tyr	Val	Leu
			645						650					655	
Leu	Cys	Phe	Val	Phe	Ile	Ser	Pro	Pro	Gly	Ser	Cys	Asn	Asn	Lys	Tyr
			660					665					670		
Phe	Ala	Glu	Ile	Arg	Ser	Tyr	Gly	Trp	Trp	His	Phe	Thr	Tyr	Phe	Asn
		675					680					685			
Trp	Lys	Leu	Pro	Lys	Gln	Trp	Glu	Phe							
	690					695									

&lt;210&gt; 203

&lt;211&gt; 2082

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 203

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ttgcatctgt caatttgaat taatatctgt accttaaaaa tt

2082

&lt;210&gt; 204

&lt;211&gt; 691

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 204

Met	Lys	Ala	Pro	Ala	Val	Leu	Ala	Pro	Gly	Ile	Leu	Val	Leu	Leu	Phe
1				5					10				15		
Thr	Leu	Val	Gln	Arg	Ser	Asn	Gly	Glu	Cys	Lys	Glu	Ala	Leu	Ala	Lys
			20					25					30		
Ser	Glu	Met	Asn	Val	Asn	Met	Lys	Tyr	Gln	Leu	Pro	Asn	Phe	Thr	Ala
		35					40					45			
Glu	Thr	Pro	Ile	Gln	Asn	Val	Ile	Leu	His	Glu	His	His	Ile	Phe	Leu
		50				55				60					
Gly	Ala	Thr	Asn	Tyr	Ile	Tyr	Val	Leu	Asn	Glu	Glu	Asp	Leu	Gln	Lys
65					70					75				80	
Val	Ala	Glu	Tyr	Lys	Thr	Gly	Pro	Val	Leu	Glu	His	Pro	Asp	Cys	Phe
				85					90					95	
Pro	Cys	Gln	Asp	Cys	Ser	Ser	Lys	Ala	Asn	Leu	Ser	Gly	Gly	Val	Trp
			100					105					110		
Lys	Asp	Asn	Ile	Asn	Met	Ala	Leu	Val	Val	Asp	Thr	Tyr	Tyr	Asp	Asp
		115					120					125			
Gln	Leu	Ile	Ser	Cys	Gly	Ser	Val	Asn	Arg	Gly	Thr	Cys	Gln	Arg	His
		130				135					140				
Val	Phe	Pro	His	Asn	His	Thr	Ala	Asp	Ile	Gln	Ser	Glu	Val	His	Cys
145					150					155					160
Ile	Phe	Ser	Pro	Gln	Ile	Glu	Glu	Pro	Ser	Gln	Cys	Pro	Asp	Cys	Val
				165					170					175	
Val	Ser	Ala	Leu	Gly	Ala	Lys	Val	Leu	Ser	Ser	Val	Lys	Asp	Arg	Phe
			180					185					190		
Ile	Asn	Phe	Phe	Val	Gly	Asn	Thr	Ile	Asn	Ser	Ser	Tyr	Phe	Pro	Asp
		195					200					205			
His	Pro	Leu	His	Ser	Ile	Ser	Val	Arg	Arg	Leu	Lys	Glu	Thr	Lys	Asp
		210				215					220				
Gly	Phe	Met	Phe	Leu	Thr	Asp	Gln	Ser	Tyr	Ile	Asp	Val	Leu	Pro	Glu
225					230					235				240	
Phe	Arg	Asp	Ser	Tyr	Pro	Ile	Lys	Tyr	Val	His	Ala	Phe	Glu	Ser	Asn
				245					250					255	
Asn	Phe	Ile	Tyr	Phe	Leu	Thr	Val	Gln	Arg	Glu	Thr	Leu	Asp	Ala	Gln
			260					265					270		
Thr	Phe	His	Thr	Arg	Ile	Ile	Arg	Phe	Cys	Ser	Ile	Asn	Ser	Gly	Leu
		275					280					285			
His	Ser	Tyr	Met	Glu	Met	Pro	Leu	Glu	Cys	Ile	Leu	Thr	Glu	Lys	Arg
		290				295					300				
Lys	Lys	Arg	Ser	Thr	Lys	Lys	Glu	Val	Phe	Asn	Ile	Leu	Gln	Ala	Ala
305					310					315				320	
Tyr	Val	Ser	Lys	Pro	Gly	Ala	Gln	Leu	Ala	Arg	Gln	Ile	Gly	Ala	Ser
				325					330					335	
Leu	Asn	Asp	Asp	Ile	Leu	Phe	Gly	Val	Phe	Ala	Gln	Ser	Lys	Pro	Asp
			340					345					350		
Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser	Ala	Met	Cys	Ala	Phe	Pro	Ile	Lys
		355					360					365			
Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys	Ile	Val	Asn	Lys	Asn	Asn	Val	Arg
		370				375					380				

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Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg  
 385 390 395 400  
 Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr  
 405 410 415  
 Arg Thr Glu Phe Thr Thr Ala Leu Gln Arg Val Asp Leu Phe Met Gly  
 420 425 430  
 Gln Phe Ser Glu Val Leu Leu Thr Ser Ile Ser Thr Phe Ile Lys Gly  
 435 440 445  
 Asp Leu Thr Ile Ala Asn Leu Gly Thr Ser Glu Gly Arg Phe Met Gln  
 450 455 460  
 Val Val Val Ser Arg Ser Gly Pro Ser Thr Pro His Val Asn Phe Leu  
 465 470 475 480  
 Leu Asp Ser His Pro Val Ser Pro Glu Val Ile Val Glu His Thr Leu  
 485 490 495  
 Asn Gln Asn Gly Tyr Thr Leu Val Ile Thr Gly Lys Lys Cys Gly Trp  
 500 505 510  
 Arg His Asp Lys Cys Val Arg Ser Glu Glu Cys Leu Ser Gly Thr Trp  
 515 520 525  
 Thr Gln Gln Ile Cys Leu Pro Ala Ile Tyr Lys Val Phe Pro Asn Ser  
 530 535 540  
 Ala Pro Leu Glu Gly Gly Thr Arg Leu Thr Ile Cys Gly Trp Asp Phe  
 545 550 555 560  
 Gly Phe Arg Arg Asn Asn Lys Phe Asp Leu Lys Lys Thr Arg Val Leu  
 565 570 575  
 Leu Gly Asn Glu Ser Cys Thr Leu Thr Leu Ser Glu Ser Thr Met Asn  
 580 585 590  
 Thr Leu Lys Cys Thr Val Gly Pro Ala Met Asn Lys His Phe Asn Met  
 595 600 605  
 Ser Ile Ile Ile Ser Asn Gly His Gly Thr Thr Gln Tyr Ser Thr Phe  
 610 615 620  
 Ser Tyr Val Asp Pro Val Ile Thr Ser Ile Ser Pro Lys Tyr Gly Pro  
 625 630 635 640  
 Met Ala Gly Gly Thr Leu Leu Thr Leu Thr Gly Asn Tyr Leu Asn Ser  
 645 650 655  
 Gly Asn Ser Arg His Ile Ser Ile Gly Gly Lys Thr Cys Thr Leu Lys  
 660 665 670  
 Arg Cys Gly Lys Phe Ile Phe Cys Cys Ile Cys Gln Phe Glu Leu Ile  
 675 680 685  
 Ser Val Pro  
 690

&lt;210&gt; 205

&lt;211&gt; 2294

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 205

atgaaggccc ccgctgtgct tgcacctggc atcctcgtgc tcctgtttac cttgggtgcag 60  
 aggagcaatg gggagtgtaa agaggcacta gcaaagtcag agatgaatgt gaatatgaag 120  
 tatcagcttc ccaacttcac cgcggaaaca cccatccaga atgtcattct acatgagcat 180  
 cacattttcc ttgggtgccac taactacatt tatgttttaa atgaggaaga ccttcagaag 240  
 gttgctgagt acaagactgg gcctgtgctg gaacaccag attgtttccc atgtcaggac 300  
 tgcagcagca aagccaattt atcaggaggt gtttgaaaag ataacatcaa catgggtcta 360  
 gttgtcgaca cctactatga tgatcaactc attagctgtg gcagcgtcaa cagagggacc 420  
 tgccagcgac atgtctttcc ccacaatcat actgctgaca tacagtcgga gggtcactgc 480

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atattctccc cacagataga agagcccagc cagtgtcctg actgtgtggt gagegcccctg 540
ggagccaaag tcctttcatc tgtaaaggac cggttcatca acttctttgt aggcaatacc 600
ataaattctt cttatttccc agatcatcca ttgcattcga tatcagttag aaggctaaag 660
gaaacgaaag atggttttat gtttttgacg gaccagtcct acattgatgt ttacctgag 720
ttcagagatt cttaccccat taagtatgtc catgcctttg aaagcaacaa tttattttac 780
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gccatgtgtg cattccctat caaatatgtc aacgacttct tcaacaagat cgtcaacaaa 1140
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tacacactgg ttatcactgg gaagaagatc gcgaagatcc cattgaatgg cttgggttgc 1560
agacatttcc agtctgcag tcaatgcctc tctgccccac ctttgttca gtgtggctgg 1620
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acattgaaat gcacagttgg tcctgccatg aataagcatt tcaatatgtc cataattatt 1920
tcaaatggcc acgggacaac acagtacagt acattctcct atgtgctccc ctccaggatc 1980
ctgtaataac aagtatttct ccgaaatacg gtcctatggc tgggtggcact ttacttactt 2040
taactggaaa ttacctaaac agtgggaatt ctgacacat ttcaatttgt ggaaaaacat 2100
gtactttaaa aagtgtgtca aacagtattc ttgaatgtta taccacagcc caaacattt 2160
caactgagtt tgctgttaaa ttgaaaattg acttagccaa ccgagagaca agcatcttca 2220
gttaccgtga agatcccat gtctatgaaa ttcattcaac caaatctttt attaggttaag 2280
tagaagcttc tgat 2294

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&lt;210&gt; 206

&lt;211&gt; 661

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 206

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Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
1      5      10      15
Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys
20      25      30
Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
35      40      45
Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
50      55      60
Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
65      70      75      80
Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
85      90      95
Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
100     105     110
Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
115     120     125
Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
130     135     140

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Val	Phe	Pro	His	Asn	His	Thr	Ala	Asp	Ile	Gln	Ser	Glu	Val	His	Cys
145					150					155					160
Ile	Phe	Ser	Pro	Gln	Ile	Glu	Glu	Pro	Ser	Gln	Cys	Pro	Asp	Cys	Val
				165					170						175
Val	Ser	Ala	Leu	Gly	Ala	Lys	Val	Leu	Ser	Ser	Val	Lys	Asp	Arg	Phe
			180					185					190		
Ile	Asn	Phe	Phe	Val	Gly	Asn	Thr	Ile	Asn	Ser	Ser	Tyr	Phe	Pro	Asp
		195					200					205			
His	Pro	Leu	His	Ser	Ile	Ser	Val	Arg	Arg	Leu	Lys	Glu	Thr	Lys	Asp
	210					215					220				
Gly	Phe	Met	Phe	Leu	Thr	Asp	Gln	Ser	Tyr	Ile	Asp	Val	Leu	Pro	Glu
225					230					235					240
Phe	Arg	Asp	Ser	Tyr	Pro	Ile	Lys	Tyr	Val	His	Ala	Phe	Glu	Ser	Asn
				245					250						255
Asn	Phe	Ile	Tyr	Phe	Leu	Thr	Val	Gln	Arg	Glu	Thr	Leu	Asp	Ala	Gln
			260					265					270		
Thr	Phe	His	Thr	Arg	Ile	Ile	Arg	Phe	Cys	Ser	Ile	Asn	Ser	Gly	Leu
		275					280						285		
His	Ser	Tyr	Met	Glu	Met	Pro	Leu	Glu	Cys	Ile	Leu	Thr	Glu	Lys	Arg
	290					295					300				
Lys	Lys	Arg	Ser	Thr	Lys	Lys	Glu	Val	Phe	Asn	Ile	Leu	Gln	Ala	Ala
305					310					315					320
Tyr	Val	Ser	Lys	Pro	Gly	Ala	Gln	Leu	Ala	Arg	Gln	Ile	Gly	Ala	Ser
				325					330						335
Leu	Asn	Asp	Asp	Ile	Leu	Phe	Gly	Val	Phe	Ala	Gln	Ser	Lys	Pro	Asp
			340					345						350	
Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser	Ala	Met	Cys	Ala	Phe	Pro	Ile	Lys
		355					360					365			
Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys	Ile	Val	Asn	Lys	Asn	Asn	Val	Arg
	370					375					380				
Cys	Leu	Gln	His	Phe	Tyr	Gly	Pro	Asn	His	Glu	His	Cys	Phe	Asn	Arg
385					390					395					400
Thr	Leu	Leu	Arg	Asn	Ser	Ser	Gly	Cys	Glu	Ala	Arg	Arg	Asp	Glu	Tyr
				405					410					415	
Arg	Thr	Glu	Phe	Thr	Thr	Ala	Leu	Gln	Arg	Val	Asp	Leu	Phe	Met	Gly
			420					425					430		
Gln	Phe	Ser	Glu	Val	Leu	Leu	Thr	Ser	Ile	Ser	Thr	Phe	Ile	Lys	Gly
		435					440					445			
Asp	Leu	Thr	Ile	Ala	Asn	Leu	Gly	Thr	Ser	Glu	Gly	Arg	Phe	Met	Gln
	450					455					460				
Val	Val	Val	Ser	Arg	Ser	Gly	Pro	Ser	Thr	Pro	His	Val	Asn	Phe	Leu
465					470					475					480
Leu	Asp	Ser	His	Pro	Val	Ser	Pro	Glu	Val	Ile	Val	Glu	His	Thr	Leu
				485					490					495	
Asn	Gln	Asn	Gly	Tyr	Thr	Leu	Val	Ile	Thr	Gly	Lys	Lys	Ile	Ala	Lys
			500					505					510		
Ile	Pro	Leu	Asn	Gly	Leu	Gly	Cys	Arg	His	Phe	Gln	Ser	Cys	Ser	Gln
		515					520					525			
Cys	Leu	Ser	Ala	Pro	Pro	Phe	Val	Gln	Cys	Gly	Trp	Cys	His	Asp	Lys
	530					535					540				
Cys	Val	Arg	Ser	Glu	Glu	Cys	Leu	Ser	Gly	Thr	Trp	Thr	Gln	Gln	Ile
545					550					555					560
Cys	Leu	Pro	Ala	Ile	Tyr	Lys	Val	Phe	Pro	Asn	Ser	Ala	Pro	Leu	Glu
				565					570					575	
Gly	Gly	Thr	Arg	Leu	Thr	Ile	Cys	Gly	Trp	Asp	Phe	Gly	Phe	Arg	Arg
			580					585					590		

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Asn	Asn	Lys	Phe	Asp	Leu	Lys	Lys	Thr	Arg	Val	Leu	Leu	Gly	Asn	Glu
		595					600					605			
Ser	Cys	Thr	Leu	Thr	Leu	Ser	Glu	Ser	Thr	Met	Asn	Thr	Leu	Lys	Cys
	610					615					620				
Thr	Val	Gly	Pro	Ala	Met	Asn	Lys	His	Phe	Asn	Met	Ser	Ile	Ile	Ile
625					630					635				640	
Ser	Asn	Gly	His	Gly	Thr	Thr	Gln	Tyr	Ser	Thr	Phe	Ser	Tyr	Val	Leu
				645					650					655	
Pro	Ser	Arg	Ile	Leu											
			660												

&lt;210&gt; 207

&lt;211&gt; 3256

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 207

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tatcagcttc ccaacttcac cgcggaaaca cccatccaga atgtcattct acatgagcat 180
cacattttcc ttggtgccac taactacatt tatgttttaa atgaggaaga ccttcagaag 240
gttgctgagt acaagactgg gcctgtgctg gaacaccagc attgtttccc atgtcaggac 300
tgcagcagca aagccaattt atcaggaggt gtttggaag ataacatcaa catggctcta 360
gttgctcgaca cctactatga tgatcaactc attagctgtg gcagcgtcaa cagagggacc 420
tgccagcgac atgtctttcc ccacaatcat actgctgaca tacagtcgga gggtcactgc 480
atattctccc cacagataga agagcccagc cagtgtcctg actgtgtggt gagcgccctg 540
ggagccaaag tcctttcatc tgtaaaggac cggttcatca acttctttgt aggcaatacc 600
ataaattctt cttatttccc agatcatcca ttgcattcga tatcagttag aaggctaaag 660
gaaacgaaag atggttttat gtttttgacg gaccagtcct acattgatgt tttacctgag 720
ttcagagatt cttaccccat taagtatgtc catgcctttg aaagcaacaa ttttatttac 780
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tatgtcagca agcctggggc ccagcttgct agacaaatag gagccagcct gaatgatgac 1020
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gatcccattg tctatgtaat tcatccaacc aaatctttta ttaggttaagt agaagcttct 2280

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agttaatttc cttgca 3256

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&lt;210&gt; 208

&lt;211&gt; 755

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 208

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Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
 1          5          10          15
Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys
          20          25          30
Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
          35          40          45
Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
          50          55          60
Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
          65          70          75          80
Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
          85          90          95
Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
          100          105          110
Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
          115          120          125
Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
          130          135          140
Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys
          145          150          155          160
Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val
          165          170          175
Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe
          180          185          190
Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp
          195          200          205
His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp
          210          215          220
Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu
          225          230          235          240
Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn
          245          250          255

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Asn	Phe	Ile	Tyr	Phe	Leu	Thr	Val	Gln	Arg	Glu	Thr	Leu	Asp	Ala	Gln
			260					265					270		
Thr	Phe	His	Thr	Arg	Ile	Ile	Arg	Phe	Cys	Ser	Ile	Asn	Ser	Gly	Leu
			275				280					285			
His	Ser	Tyr	Met	Glu	Met	Pro	Leu	Glu	Cys	Ile	Leu	Thr	Glu	Lys	Arg
			290			295					300				
Lys	Lys	Arg	Ser	Thr	Lys	Lys	Glu	Val	Phe	Asn	Ile	Leu	Gln	Ala	Ala
					310					315					320
Tyr	Val	Ser	Lys	Pro	Gly	Ala	Gln	Leu	Ala	Arg	Gln	Ile	Gly	Ala	Ser
				325					330					335	
Leu	Asn	Asp	Asp	Ile	Leu	Phe	Gly	Val	Phe	Ala	Gln	Ser	Lys	Pro	Asp
			340					345					350		
Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser	Ala	Met	Cys	Ala	Phe	Pro	Ile	Lys
			355				360					365			
Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys	Ile	Val	Asn	Lys	Asn	Asp	Val	Arg
			370			375				380					
Cys	Leu	Gln	His	Phe	Tyr	Gly	Pro	Asn	His	Glu	His	Cys	Phe	Asn	Gly
					390					395					400
Thr	Leu	Leu	Arg	Asn	Ser	Ser	Gly	Cys	Glu	Ala	Arg	Arg	Asp	Glu	Tyr
				405				410					415		
Arg	Thr	Glu	Phe	Thr	Thr	Ala	Leu	Gln	Arg	Val	Asp	Leu	Phe	Met	Gly
			420					425				430			
Gln	Phe	Ser	Glu	Val	Leu	Leu	Thr	Ser	Ile	Ser	Thr	Phe	Ile	Lys	Gly
			435				440					445			
Asp	Leu	Thr	Ile	Ala	Asn	Leu	Gly	Thr	Ser	Glu	Gly	Arg	Phe	Met	Gln
	450				455					460					
Val	Val	Val	Ser	Arg	Ser	Gly	Pro	Ser	Thr	Pro	Arg	Val	Asn	Phe	Leu
					470					475					480
Leu	Asp	Ser	His	Pro	Val	Ser	Pro	Glu	Val	Ile	Val	Glu	His	Thr	Leu
				485					490					495	
Asn	Gln	Asn	Gly	Tyr	Thr	Leu	Val	Ile	Thr	Gly	Lys	Lys	Ile	Thr	Lys
			500				505						510		
Ile	Pro	Leu	Asn	Gly	Leu	Gly	Cys	Arg	His	Phe	Gln	Ser	Cys	Ser	Gln
			515				520					525			
Cys	Leu	Ser	Ala	Pro	Pro	Phe	Val	Gln	Cys	Gly	Trp	Cys	Tyr	Asp	Lys
			530			535					540				
Cys	Val	Arg	Ser	Glu	Glu	Cys	Leu	Ser	Gly	Thr	Trp	Thr	Gln	Gln	Ile
				545		550				555					560
Cys	Leu	Pro	Ala	Ile	Tyr	Lys	Val	Phe	Pro	Asn	Ser	Ala	Pro	Leu	Glu
				565					570					575	
Gly	Gly	Thr	Arg	Leu	Thr	Ile	Cys	Gly	Trp	Asp	Phe	Gly	Phe	Arg	Arg
			580					585					590		
Asn	Asn	Lys	Phe	Asp	Leu	Lys	Lys	Thr	Arg	Val	Leu	Leu	Gly	Asn	Glu
			595				600					605			
Ser	Cys	Thr	Leu	Thr	Leu	Ser	Glu	Ser	Thr	Met	Asn	Thr	Ser	Lys	Cys
			610			615					620				
Thr	Val	Gly	Pro	Ala	Met	Asn	Lys	His	Phe	Asn	Met	Ser	Ile	Ile	Ile
				625		630				635					640
Ser	Asn	Gly	His	Gly	Thr	Thr	Gln	Tyr	Ser	Thr	Phe	Ser	Tyr	Val	Asp
				645					650					655	
Pro	Val	Ile	Thr	Ser	Ile	Ser	Pro	Lys	Tyr	Gly	Pro	Met	Ala	Gly	Gly
				660				665					670		
Thr	Leu	Leu	Thr	Leu	Thr	Gly	Asn	Tyr	Leu	Asn	Ser	Gly	Asn	Ser	Arg
			675				680					685			
His	Ile	Ser	Ile	Gly	Gly	Lys	Thr	Cys	Thr	Leu	Lys	Ser	Val	Ser	Asn
			690			695					700				

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Ser Ile Leu Glu Cys Tyr Thr Pro Ala Gln Thr Ile Ser Thr Glu Phe  
 705 710 715 720  
 Ala Val Lys Leu Lys Ile Asp Leu Ala Asn Arg Glu Thr Ser Ile Phe  
 725 730 735  
 Ser Tyr Arg Glu Asp Pro Ile Val Tyr Val Ile His Pro Thr Lys Ser  
 740 745 750  
 Phe Ile Arg  
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&lt;210&gt; 209

&lt;211&gt; 2481

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 209

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gcacatctttgc ctctaaccat gtggctttca tggtagctga gacatctcag tttcgccctt 2460  
aagggtttgct agttaatttc c 2481

&lt;210&gt; 210

&lt;211&gt; 823

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 210

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Thr	Leu	Val	Gln	Arg	Ser	Asn	Gly	Glu	Cys	Lys	Glu	Ala	Leu	Ala	Lys
			20					25					30		
Ser	Glu	Met	Asn	Val	Asn	Thr	Lys	Tyr	Gln	Leu	Pro	Asn	Phe	Thr	Ala
		35					40					45			
Glu	Thr	Pro	Ile	Gln	Asn	Val	Ile	Leu	His	Glu	His	His	Ile	Phe	Leu
	50					55					60				
Gly	Ala	Thr	Asn	Tyr	Ile	Tyr	Val	Leu	Asn	Glu	Glu	Asp	Leu	Gln	Lys
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Val	Ala	Glu	Tyr	Lys	Thr	Gly	Pro	Val	Leu	Glu	His	Pro	Asp	Cys	Phe
				85					90					95	
Pro	Cys	Gln	Asp	Cys	Ser	Ser	Lys	Ala	Asn	Leu	Ser	Gly	Gly	Val	Trp
			100					105					110		
Lys	Asp	Asn	Ile	Asn	Met	Ala	Leu	Val	Val	Asp	Thr	Tyr	Tyr	Asp	Asp
		115					120					125			
Gln	Leu	Ile	Ser	Cys	Gly	Ser	Val	Asn	Arg	Gly	Thr	Cys	Gln	Arg	His
	130					135					140				
Val	Phe	Pro	His	Asn	His	Thr	Ala	Asp	Ile	Gln	Ser	Glu	Val	His	Cys
145					150					155				160	
Ile	Phe	Ser	Pro	Gln	Ile	Glu	Glu	Pro	Ser	Gln	Cys	Pro	Asp	Cys	Val
				165					170					175	
Val	Ser	Ala	Leu	Gly	Ala	Lys	Val	Leu	Ser	Ser	Val	Lys	Asp	Arg	Phe
			180					185					190		
Ile	Asn	Phe	Phe	Val	Gly	Asn	Thr	Ile	Asn	Ser	Ser	Tyr	Phe	Pro	Asp
		195					200					205			
His	Pro	Leu	His	Ser	Ile	Ser	Val	Arg	Arg	Leu	Lys	Glu	Thr	Lys	Asp
	210					215					220				
Gly	Phe	Met	Phe	Leu	Thr	Asp	Gln	Ser	Tyr	Ile	Asp	Val	Leu	Pro	Glu
225					230					235				240	
Phe	Arg	Asp	Ser	Tyr	Pro	Ile	Lys	Tyr	Val	His	Ala	Phe	Glu	Ser	Asn
				245					250					255	
Asn	Phe	Ile	Tyr	Phe	Leu	Thr	Val	Gln	Arg	Glu	Thr	Leu	Asp	Ala	Gln
			260					265					270		
Thr	Phe	His	Thr	Arg	Ile	Ile	Arg	Phe	Cys	Ser	Ile	Asn	Ser	Gly	Leu
		275					280					285			
His	Ser	Tyr	Met	Glu	Met	Pro	Leu	Glu	Cys	Ile	Leu	Thr	Glu	Lys	Arg
	290					295					300				
Lys	Lys	Arg	Ser	Thr	Lys	Lys	Glu	Val	Phe	Asn	Ile	Leu	Gln	Ala	Ala
					310					315				320	
Tyr	Val	Ser	Lys	Pro	Gly	Ala	Gln	Leu	Ala	Arg	Gln	Ile	Gly	Ala	Ser
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Leu	Asn	Asp	Asp	Ile	Leu	Phe	Gly	Val	Phe	Ala	Gln	Ser	Lys	Pro	Asp
			340					345					350		
Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser	Ala	Met	Cys	Ala	Phe	Pro	Ile	Lys
		355					360					365			
Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys	Ile	Val	Asn	Lys	Asn	Asn	Val	Arg



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820

&lt;210&gt; 211

&lt;211&gt; 2667

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 211

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&lt;210&gt; 212



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&lt;211&gt; 877

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 212

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Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
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Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys
          20          25          30
Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
          35          40          45
Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
          50          55          60
Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
65          70          75          80
Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
          85          90          95
Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
          100          105          110
Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
          115          120          125
Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
          130          135          140
Val Phe Pro Arg Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys
145          150          155          160
Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val
          165          170          175
Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe
          180          185          190
Thr Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp
          195          200          205
His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp
          210          215          220
Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu
225          230          235          240
Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn
          245          250          255
Asn Phe Ile Tyr Phe Leu Thr Val Gln Arg Glu Thr Leu Asp Ala Gln
          260          265          270
Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Ile Asn Ser Gly Leu
          275          280          285
His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg
          290          295          300
Lys Lys Arg Ser Thr Lys Lys Glu Val Phe Asn Ile Leu Gln Ala Ala
305          310          315          320
Tyr Val Ser Lys Pro Gly Ala Gln Leu Ala Arg Gln Ile Gly Ala Ser
          325          330          335
Pro Asn Asp Asp Ile Leu Phe Gly Val Phe Ala Gln Ser Lys Pro Asp
          340          345          350
Ser Ala Glu Pro Met Asp Arg Ser Ala Met Cys Ala Phe Pro Ile Lys
          355          360          365
Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Asn Val Arg
          370          375          380
Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg
385          390          395          400
Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr

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Arg	Thr	Glu	Phe	Thr	Thr	Ala	Leu	Gln	Arg	Val	Asp	Leu	Phe	Met	Gly		
			420					425					430				
Gln	Phe	Ser	Glu	Val	Leu	Leu	Thr	Ser	Ile	Ser	Thr	Phe	Ile	Lys	Gly		
		435					440					445					
Asp	Leu	Thr	Ile	Ala	Asn	Leu	Gly	Thr	Ser	Glu	Gly	Arg	Phe	Met	Gln		
	450					455					460						
Val	Val	Val	Ser	Arg	Ser	Gly	Pro	Ser	Thr	Pro	His	Val	Asn	Phe	Leu		
465					470					475					480		
Leu	Asp	Ser	His	Pro	Val	Ser	Pro	Glu	Val	Ile	Val	Glu	His	Thr	Leu		
			485					490							495		
Asn	Gln	Asn	Gly	Tyr	Thr	Leu	Val	Ile	Thr	Gly	Lys	Lys	Ile	Thr	Lys		
		500						505					510				
Ile	Pro	Leu	Asn	Gly	Leu	Gly	Cys	Arg	His	Phe	Gln	Ser	Cys	Ser	Gln		
		515					520					525					
Cys	Leu	Ser	Ala	Pro	Pro	Phe	Val	Gln	Cys	Gly	Trp	Cys	His	Asp	Lys		
	530					535					540						
Cys	Val	Arg	Ser	Glu	Glu	Cys	Leu	Ser	Gly	Thr	Trp	Thr	Gln	Gln	Ile		
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Cys	Leu	Pro	Ala	Ile	Tyr	Lys	Val	Phe	Pro	Asn	Ser	Ala	Pro	Leu	Glu		
			565					570							575		
Gly	Gly	Thr	Arg	Leu	Thr	Ile	Cys	Gly	Trp	Asp	Phe	Gly	Phe	Arg	Arg		
		580						585					590				
Asn	Asn	Lys	Phe	Asp	Leu	Lys	Lys	Thr	Arg	Val	Leu	Leu	Gly	Asn	Glu		
		595					600					605					
Ser	Cys	Thr	Leu	Thr	Leu	Ser	Glu	Ser	Thr	Met	Asn	Thr	Leu	Lys	Cys		
	610					615					620						
Thr	Val	Gly	Pro	Ala	Met	Asn	Lys	His	Phe	Asn	Met	Ser	Ile	Ile	Ile		
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			645					650							655		
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Thr	Leu	Leu	Thr	Leu	Thr	Gly	Asn	Tyr	Leu	Asn	Ser	Gly	Asn	Ser	Arg		
	675						680					685					
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	690					695					700						
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705					710				715						720		
Ala	Val	Lys	Leu	Lys	Ile	Asp	Leu	Ala	Asn	Arg	Glu	Thr	Ser	Ile	Phe		
			725					730							735		
Ser	Tyr	Arg	Glu	Asp	Pro	Ile	Val	Tyr	Glu	Ile	His	Pro	Thr	Lys	Ser		
		740						745					750				
Phe	Ile	Ser	Gly	Gly	Ser	Thr	Ile	Thr	Gly	Val	Gly	Lys	Asn	Leu	Asn		
	755						760					765					
Ser	Val	Ser	Val	Pro	Arg	Met	Val	Ile	Asn	Val	His	Glu	Ala	Gly	Arg		
	770					775					780						
Asn	Phe	Thr	Val	Ala	Cys	Gln	His	Arg	Ser	Asn	Ser	Glu	Ile	Ile	Cys		
785					790					795					800		
Cys	Thr	Thr	Pro	Ser	Leu	Gln	Gln	Leu	Asn	Leu	Gln	Leu	Pro	Leu	Lys		
			805					810							815		
Thr	Lys	Ala	Phe	Phe	Met	Leu	Asp	Gly	Ile	Leu	Ser	Lys	Tyr	Phe	Asp		
		820						825					830				
Leu	Ile	Tyr	Val	His	Asn	Pro	Val	Phe	Lys	Pro	Phe	Glu	Lys	Pro	Val		
		835					840					845					
Met	Ile	Ser	Met	Gly	Asn	Glu	Asn	Val	Leu	Glu	Ile	Lys	Val	Arg	Asn		

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 <212> DNA  
 <213> Homo Sapiens

<400> 213  
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 cacattttcc ttggtgccac taactacatt tatgttttaa atgaggaaga ccttcagaag 240  
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 <212> PRT  
 <213> Homo Sapiens

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 Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp  
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 Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp  
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 Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys  
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 Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val  
 165 170 175  
 Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe  
 180 185 190  
 Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp  
 195 200 205  
 His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp  
 210 215 220  
 Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Ala Leu Pro Glu  
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 His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg  
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 Lys Lys Arg Ser Thr Lys Lys Glu Val Phe Asn Ile Leu Gln Ala Ala  
 305 310 315 320  
 Tyr Val Ser Lys Pro Gly Ala Gln Leu Ala Arg Gln Ile Gly Ala Ser  
 325 330 335  
 Leu Asn Asp Asp Ile Leu Phe Gly Val Phe Ala Gln Ser Lys Pro Asp  
 340 345 350  
 Ser Ala Glu Pro Met Asp Arg Ser Ala Met Cys Ala Phe Pro Ile Lys  
 355 360 365  
 Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Asn Val Arg  
 370 375 380  
 Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg  
 385 390 395 400  
 Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr

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Leu	Asp	Ser	His	Pro	Val	Ser	Pro	Glu	Val	Ile	Val	Glu	His	Thr	Leu								
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Asn	Gln	Asn	Gly	Tyr	Thr	Leu	Val	Ile	Thr	Gly	Arg	Lys	Ile	Thr	Lys								
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Cys	Leu	Pro	Ala	Ile	Tyr	Lys	Val	Phe	Pro	Asn	Ser	Ala	Pro	Leu	Glu								
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Ser	Cys	Thr	Leu	Thr	Leu	Ser	Glu	Ser	Thr	Met	Asn	Thr	Leu	Lys	Cys								
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Pro	Val	Ile	Thr	Ser	Ile	Ser	Pro	Lys	Tyr	Gly	Pro	Met	Ala	Gly	Gly								
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Thr	Leu	Leu	Thr	Leu	Thr	Gly	Asn	Tyr	Leu	Asn	Ser	Gly	Asn	Ser	Arg								
				675				680				685											
His	Ile	Ser	Ile	Gly	Gly	Lys	Thr	Cys	Thr	Leu	Lys	Ser	Val	Ser	Asn								
				690				695				700											
Ser	Ile	Leu	Glu	Cys	Tyr	Thr	Pro	Ala	Gln	Thr	Ile	Ser	Thr	Glu	Ser								
				705				710				715				720							
Ala	Val	Lys	Leu	Lys	Ile	Asp	Leu	Ala	Asn	Arg	Glu	Thr	Ser	Ile	Phe								
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Ser	Tyr	Arg	Glu	Asp	Pro	Ile	Val	Tyr	Glu	Ile	His	Pro	Thr	Lys	Ser								
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Phe	Ile	Arg	His	Val	Asn	Ile	Ala	Leu	Ile	Gln	Arg												
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<212> DNA
<213> Homo Sapiens
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&lt;210&gt; 216

&lt;211&gt; 541

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 216

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Met Glu Leu Leu Pro Pro Leu Pro Gln Ser Phe Leu Leu Leu Leu Leu
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Pro Tyr Ala Ala Ser Arg Asp Phe Asp Val Lys Tyr Val Val Pro Ser
 35      40      45
Phe Ser Ala Gly Gly Leu Val Gln Ala Met Val Thr Tyr Glu Gly Asp
 50      55      60
Arg Asn Glu Ser Ala Val Phe Val Ala Ile Arg Asn Arg Leu His Val
 65      70      75      80
Leu Gly Pro Asp Leu Lys Ser Val Gln Ser Leu Ala Thr Gly Pro Ala
 85      90      95
Gly Asp Pro Gly Cys Gln Thr Cys Ala Ala Cys Gly Pro Gly Pro His
100      105      110
Gly Pro Pro Gly Asp Thr Asp Thr Lys Val Leu Val Leu Asp Pro Ala
115      120      125
Leu Pro Ala Leu Val Ser Cys Gly Ser Ser Leu Gln Gly Arg Cys Phe
130      135      140
Leu His Asp Leu Glu Pro Gln Gly Thr Ala Val His Leu Ala Ala Pro
145      150      155      160
Ala Cys Leu Phe Ser Ala His His Asn Arg Pro Asp Asp Cys Pro Asp
165      170      175
Cys Val Ala Ser Pro Leu Gly Thr Arg Val Thr Val Val Glu Gln Gly
180      185      190
Gln Ala Ser Tyr Phe Tyr Val Ala Ser Ser Leu Asp Ala Ala Val Ala
195      200      205
Ala Ser Phe Ser Pro Arg Ser Val Ser Ile Arg Arg Leu Lys Ala Asp
210      215      220
Ala Ser Gly Phe Ala Pro Gly Phe Val Ala Leu Ser Val Leu Pro Lys
225      230      235      240
His Leu Val Ser Tyr Ser Ile Glu Tyr Val His Ser Phe His Thr Gly
245      250      255
Ala Phe Val Tyr Phe Leu Thr Val Gln Pro Ala Ser Val Thr Asp Asp
260      265      270
Pro Ser Ala Leu His Thr Arg Leu Ala Arg Leu Ser Ala Thr Glu Pro
275      280      285
Glu Leu Gly Asp Tyr Arg Glu Leu Val Leu Asp Cys Arg Phe Ala Pro
290      295      300
Lys Arg Arg Arg Arg Gly Ala Pro Glu Gly Gly Gln Pro Tyr Pro Val
305      310      315      320
Leu Arg Val Ala His Ser Ala Pro Val Gly Ala Gln Leu Ala Thr Glu
325      330      335
Leu Ser Ile Ala Glu Gly Gln Glu Val Leu Phe Gly Val Phe Val Thr
340      345      350
Gly Lys Asp Gly Gly Pro Gly Val Gly Pro Asn Ser Val Val Cys Ala
355      360      365
Phe Pro Ile Asp Leu Leu Asp Thr Leu Ile Asp Glu Gly Val Glu Arg
370      375      380
Cys Cys Glu Ser Pro Val His Pro Gly Leu Arg Arg Gly Leu Asp Phe
385      390      395      400
Phe Gln Ser Pro Ser Phe Cys Pro Asn Pro Val Phe Gln Val Pro Ile
405      410      415
Gln Gly Pro Gly Cys Arg His Phe Leu Thr Cys Gly Arg Cys Leu Arg
420      425      430
Ala Trp His Phe Met Gly Cys Gly Trp Cys Gly Asn Met Cys Gly Gln
435      440      445

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			485						490					495	
Pro	Glu	Gly	Thr	His	Gln	Val	Thr	Val	Gly	Gln	Ser	Pro	Cys	Arg	Pro
			500					505					510		
Leu	Pro	Lys	Asp	Ser	Ser	Lys	Leu	Arg	Tyr	Asn	Leu	Val	Pro	Pro	Leu
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Pro	Phe	Pro	Glu	Gly	Gly	Asn	Gln	Ala	Ala	Pro	Ser	Pro			
530						535					540				

&lt;210&gt; 217

&lt;211&gt; 3069

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 217

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&lt;210&gt; 218

&lt;211&gt; 908

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 218

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Met Glu Leu Leu Pro Pro Leu Pro Gln Ser Phe Leu Leu Leu Leu Leu
 1          5          10          15
Leu Pro Ala Lys Pro Ala Ala Gly Glu Asp Trp Gln Cys Pro Arg Thr
 20          25          30
Pro Tyr Ala Ala Ser Arg Asp Phe Asp Val Lys Tyr Val Val Pro Ser
 35          40          45
Phe Ser Ala Gly Gly Leu Val Gln Ala Met Val Thr Tyr Glu Gly Asp
 50          55          60
Arg Asn Glu Ser Ala Val Phe Val Ala Ile Arg Asn Arg Leu His Val
 65          70          75          80
Leu Gly Pro Asp Leu Lys Ser Val Gln Ser Leu Ala Thr Gly Pro Ala
 85          90          95
Gly Asp Pro Gly Cys Gln Thr Cys Ala Ala Cys Gly Pro Gly Pro His
100          105          110
Gly Pro Pro Gly Asp Thr Asp Thr Lys Val Leu Val Leu Asp Pro Ala
115          120          125
Leu Pro Ala Leu Val Ser Cys Gly Ser Ser Leu Gln Gly Arg Cys Phe
130          135          140
Leu His Asp Leu Glu Pro Gln Gly Thr Ala Val His Leu Ala Ala Pro
145          150          155          160
Ala Cys Leu Phe Ser Ala His His Asn Arg Pro Asp Asp Cys Pro Asp
165          170          175
Cys Val Ala Ser Pro Leu Gly Thr Arg Val Thr Val Val Glu Gln Gly
180          185          190
Gln Ala Ser Tyr Phe Tyr Val Ala Ser Ser Leu Asp Ala Ala Val Ala
195          200          205
Ala Ser Phe Ser Pro Arg Ser Val Ser Ile Arg Arg Leu Lys Ala Asp
210          215          220
Ala Ser Gly Phe Ala Pro Gly Phe Val Ala Leu Ser Val Leu Pro Lys
225          230          235          240
His Leu Val Ser Tyr Ser Ile Glu Tyr Val His Ser Phe His Thr Gly
245          250          255
Ala Phe Val Tyr Phe Leu Thr Val Gln Pro Ala Ser Val Thr Asp Asp

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			260					265				270			
Pro	Ser	Ala	Leu	His	Thr	Arg	Leu	Ala	Arg	Leu	Ser	Ala	Thr	Glu	Pro
		275					280					285			
Glu	Leu	Gly	Asp	Tyr	Arg	Glu	Leu	Val	Leu	Asp	Cys	Arg	Phe	Ala	Pro
		290				295					300				
Lys	Arg	Arg	Arg	Arg	Gly	Ala	Pro	Glu	Gly	Gly	Gln	Pro	Tyr	Pro	Val
305					310					315					320
Leu	Arg	Val	Ala	His	Ser	Ala	Pro	Val	Gly	Ala	Gln	Leu	Ala	Thr	Glu
				325					330						335
Leu	Ser	Ile	Ala	Glu	Gly	Gln	Glu	Val	Leu	Phe	Gly	Val	Phe	Val	Thr
			340					345					350		
Gly	Lys	Asp	Gly	Gly	Pro	Gly	Val	Gly	Pro	Asn	Ser	Val	Val	Cys	Ala
		355					360					365			
Phe	Pro	Ile	Asp	Leu	Leu	Asp	Thr	Leu	Ile	Asp	Glu	Gly	Val	Glu	Arg
		370				375					380				
Cys	Cys	Glu	Ser	Pro	Val	His	Pro	Gly	Leu	Arg	Arg	Gly	Leu	Asp	Phe
385					390					395					400
Phe	Gln	Ser	Pro	Ser	Phe	Cys	Pro	Asn	Pro	Pro	Gly	Leu	Glu	Ala	Leu
				405					410						415
Ser	Pro	Asn	Thr	Ser	Cys	Arg	His	Phe	Pro	Leu	Leu	Val	Ser	Ser	Ser
			420					425					430		
Phe	Ser	Arg	Val	Asp	Leu	Phe	Asn	Gly	Leu	Leu	Gly	Pro	Val	Gln	Val
		435					440					445			
Thr	Ala	Leu	Tyr	Val	Thr	Arg	Leu	Asp	Asn	Val	Thr	Val	Ala	His	Met
						455						460			
Gly	Thr	Met	Asp	Gly	Arg	Ile	Leu	Gln	Val	Glu	Leu	Val	Arg	Ser	Leu
465					470					475					480
Asn	Tyr	Leu	Leu	Tyr	Val	Ser	Asn	Phe	Ser	Leu	Gly	Asp	Ser	Gly	Gln
				485					490					495	
Pro	Val	Gln	Arg	Asp	Val	Ser	Arg	Leu	Gly	Asp	His	Leu	Leu	Phe	Ala
			500					505					510		
Ser	Gly	Asp	Gln	Val	Phe	Gln	Val	Pro	Ile	Gln	Gly	Pro	Gly	Cys	Arg
		515					520					525			
His	Phe	Leu	Thr	Cys	Gly	Arg	Cys	Leu	Arg	Ala	Trp	His	Phe	Met	Gly
		530				535					540				
Cys	Gly	Trp	Cys	Gly	Asn	Met	Cys	Gly	Gln	Gln	Lys	Glu	Cys	Pro	Gly
545					550					555					560
Ser	Trp	Gln	Gln	Asp	His	Cys	Pro	Pro	Lys	Leu	Thr	Glu	Phe	His	Pro
				565					570					575	
His	Ser	Gly	Pro	Leu	Arg	Gly	Ser	Thr	Arg	Leu	Thr	Leu	Cys	Gly	Ser
			580					585					590		
Asn	Phe	Tyr	Leu	His	Pro	Ser	Gly	Leu	Val	Pro	Glu	Gly	Thr	His	Gln
		595					600					605			
Val	Thr	Val	Gly	Gln	Ser	Pro	Cys	Arg	Pro	Leu	Pro	Lys	Asp	Ser	Ser
						615	</								

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705					710					715					720
Gly	Thr	Glu	Cys	Leu	Leu	Ala	Arg	Val	Ser	Glu	Gly	Gln	Leu	Leu	Cys
				725					730					735	
Ala	Thr	Pro	Pro	Gly	Ala	Thr	Val	Ala	Ser	Val	Pro	Leu	Ser	Leu	Gln
			740					745					750		
Val	Gly	Gly	Ala	Gln	Val	Pro	Gly	Ser	Trp	Thr	Phe	Gln	Tyr	Arg	Glu
	755					760					765				
Asp	Pro	Val	Val	Leu	Ser	Ile	Ser	Pro	Asn	Cys	Gly	Tyr	Ile	Asn	Ser
	770					775					780				
His	Ile	Thr	Ile	Cys	Gly	Gln	His	Leu	Thr	Ser	Ala	Trp	His	Leu	Val
	785			790					795						800
Leu	Ser	Phe	His	Asp	Gly	Leu	Arg	Ala	Val	Glu	Ser	Arg	Gln	Cys	Glu
			805					810						815	
Arg	Gln	Leu	Pro	Glu	Gln	Gln	Leu	Cys	Arg	Leu	Pro	Glu	Tyr	Val	Val
		820						825					830		
Arg	Asp	Pro	Gln	Gly	Trp	Val	Ala	Gly	Asn	Leu	Ser	Ala	Arg	Gly	Asp
	835					840						845			
Gly	Ala	Ala	Gly	Phe	Thr	Leu	Pro	Gly	Phe	Arg	Phe	Leu	Pro	Pro	Pro
	850					855					860				
His	Pro	Pro	Ser	Ala	Asn	Leu	Val	Pro	Leu	Lys	Pro	Glu	Glu	His	Ala
	865				870				875						880
Ile	Lys	Phe	Glu	Val	Ser	Val	Arg	Asp	Arg	Gly	Arg	Asp	Ser	Trp	Gly
			885					890						895	
Ser	Glu	Ser	Arg	Gly	Gln	Pro	Thr	Gly	Trp	Ser	Ser				
			900					905							

&lt;210&gt; 219

&lt;211&gt; 3500

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 219

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gggtcccagct cgccctcgatg gagctcctcc cgccgctgcc tcagtccttc ctgttgctgc 60
tgctgttgcc tgccaagccc gcggcgggcg aggactggca gtgccgcgc accccctacg 120
cgccctctcg cgactttgac gtgaagtagc tgggtgccag cttctccgc ggaggcctgg 180
tacaggccat ggtgacctac gagggcgaca gaaatgagag tgctgtgttt gtagccatac 240
gcaatcgccct gcatgtgctt gggcctgacc tgaagtctgt ccagagcctg gccacggggc 300
ctgctggaga ccctggctgc cagacgtgtg cagcctgtgg cccaggacct cacggccctc 360
ccggtgacac agacacaaag gtgctggtgc tggatccgc gctgcctgcg ctggtcagtt 420
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tgcacctggc agcgccagcc tgccctcttc cagcccacca taaccggccc gatgactgcc 540
ccgactgtgt ggccagccca ttgggcaccc gtgtaactgt ggttgagcaa ggccaggcct 600
cctatttcta cgtggcatcc tcaactggac cagccgtggc tgccagcttc agcccacgct 660
cagtgtctat caggcgtctc aaggctgacg cctcgggatt cgcaccgggc tttgtggcgt 720
tgtcagtgct gccaagcat cttgtctcct acagtattga atacgtgcac agcttcaca 780
cgggagcctt cgtatacttc ctgactgtac agccggccag cgtgacagat gatcctagt 840
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ccctcagccc caacaccagc tgccgccact tccctctgct ggtcagtagc agcttctcac 1320
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gccttgacaa cgtcacagtg gcacacatgg gcacaatgga tgggcgtatc ctgcagggtgg 1440
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ggcagcccggt gcagcgggat gtcagtcgtc ttggggacca cctactcttt gcctctgggg 1560
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ccaagggttaa tctctgcccc accagaacct tccttccatg gagggaggca tgggtggaga 2160
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gaatgtcata tcctgggtag agtggtgcgg ccaggggcag atgggggtccc acagagcacg 3420
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&lt;210&gt; 220

&lt;211&gt; 647

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 220

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Met Glu Leu Leu Pro Leu Pro Gln Ser Phe Leu Leu Leu Leu Leu
1      5      10      15
Leu Pro Ala Lys Pro Ala Ala Gly Glu Asp Trp Gln Cys Pro Arg Thr
20      25      30
Pro Tyr Ala Ala Ser Arg Asp Phe Asp Val Lys Tyr Val Val Pro Ser
35      40      45
Phe Ser Ala Gly Gly Leu Val Gln Ala Met Val Thr Tyr Glu Gly Asp
50      55      60
Arg Asn Glu Ser Ala Val Phe Val Ala Ile Arg Asn Arg Leu His Val
65      70      75      80
Leu Gly Pro Asp Leu Lys Ser Val Gln Ser Leu Ala Thr Gly Pro Ala
85      90      95
Gly Asp Pro Gly Cys Gln Thr Cys Ala Ala Cys Gly Pro Gly Pro His

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			100					105					110		
Gly	Pro	Pro	Gly	Asp	Thr	Asp	Thr	Lys	Val	Leu	Val	Leu	Asp	Pro	Ala
		115					120					125			
Leu	Pro	Ala	Leu	Val	Ser	Cys	Gly	Ser	Ser	Leu	Gln	Gly	Arg	Cys	Phe
		130				135					140				
Leu	His	Asp	Leu	Glu	Pro	Gln	Gly	Thr	Ala	Val	His	Leu	Ala	Ala	Pro
145					150					155					160
Ala	Cys	Leu	Phe	Ser	Ala	His	His	Asn	Arg	Pro	Asp	Asp	Cys	Pro	Asp
				165					170					175	
Cys	Val	Ala	Ser	Pro	Leu	Gly	Thr	Arg	Val	Thr	Val	Val	Glu	Gln	Gly
			180					185					190		
Gln	Ala	Ser	Tyr	Phe	Tyr	Val	Ala	Ser	Ser	Leu	Asp	Ala	Ala	Val	Ala
		195					200					205			
Ala	Ser	Phe	Ser	Pro	Arg	Ser	Val	Ser	Ile	Arg	Arg	Leu	Lys	Ala	Asp
		210				215						220			
Ala	Ser	Gly	Phe	Ala	Pro	Gly	Phe	Val	Ala	Leu	Ser	Val	Leu	Pro	Lys
225					230					235					240
His	Leu	Val	Ser	Tyr	Ser	Ile	Glu	Tyr	Val	His	Ser	Phe	His	Thr	Gly
				245					250					255	
Ala	Phe	Val	Tyr	Phe	Leu	Thr	Val	Gln	Pro	Ala	Ser	Val	Thr	Asp	Asp
			260					265					270		
Pro	Ser	Ala	Leu	His	Thr	Arg	Leu	Ala	Arg	Leu	Ser	Ala	Thr	Glu	Pro
		275					280					285			
Glu	Leu	Gly	Asp	Tyr	Arg	Glu	Leu	Val	Leu	Asp	Cys	Arg	Phe	Ala	Pro
		290				295					300				
Lys	Arg	Arg	Arg	Arg	Gly	Ala	Pro	Glu	Gly	Gly	Gln	Pro	Tyr	Pro	Val
305					310					315					320
Leu	Arg	Val	Ala	His	Ser	Ala	Pro	Val	Gly	Ala	Gln	Leu	Ala	Thr	Glu
				325					330					335	
Leu	Ser	Ile	Ala	Glu	Gly	Gln	Glu	Val	Leu	Phe	Gly	Val	Phe	Val	Thr
			340					345					350		
Gly	Lys	Asp	Gly	Gly	Pro	Gly	Val	Gly	Pro	Asn	Ser	Val	Val	Cys	Ala
		355					360					365			
Phe	Pro	Ile	Asp	Leu	Leu	Asp	Thr	Leu	Ile	Asp	Glu	Gly	Val	Glu	Arg
					375					380					
Cys	Cys	Glu	Ser	Pro	Val	His	Pro	Gly	Leu	Arg	Arg	Gly	Leu	Asp	Phe
385					390					395					400
Phe	Gln	Ser	Pro	Ser	Phe	Cys	Pro	Asn	Pro	Pro	Gly	Leu	Glu	Ala	Leu
				405					410					415	
Ser	Pro	Asn	Thr	Ser	Cys	Arg	His	Phe	Pro	Leu	Leu	Val	Ser	Ser	Ser
			420					425					430		
Phe	Ser	Arg	Val	Asp	Leu	Phe	Asn	Gly	Leu	Leu	Gly	Pro	Val	Gln	Val
		435					440					445			
Thr	Ala	Leu	Tyr	Val	Thr	Arg	Leu	Asp	Asn	Val	Thr	Val	Ala	His	Met

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545					550					555				560
Ser	Trp	Gln	Gln	Asp	His	Cys	Pro	Pro	Lys	Leu	Thr	Glu	Phe	His
				565					570					575
His	Ser	Gly	Pro	Leu	Arg	Gly	Ser	Thr	Arg	Leu	Thr	Leu	Cys	Gly
			580					585					590	
Asn	Phe	Tyr	Leu	His	Pro	Ser	Gly	Leu	Val	Pro	Glu	Gly	Thr	His
		595					600				605			
Val	Thr	Val	Gly	Gln	Ser	Pro	Cys	Arg	Pro	Leu	Pro	Lys	Asp	Ser
	610					615					620			
Lys	Leu	Arg	Tyr	Asn	Leu	Val	Pro	Pro	Leu	Pro	Phe	Pro	Glu	Gly
625					630					635				640
Asn	Gln	Ala	Ala	Pro	Ser	Pro								
				645										

&lt;210&gt; 221

&lt;211&gt; 2273

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 221

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catgtgggcg	cggcgggtga	cctgacgctg	ctggccaacc	tgcggtcac	ggacccccag	120
cgcttcttcc	tgacttgctg	gtctggggag	gccggggcgg	ggaggggctc	ggacgcctgg	180
ggcccccccc	tgctgctgga	gaaggacgac	cgtatcgtgc	gcacccccgc	cgggccaccc	240
ctgcgcctgg	cgcgcaacgg	ttcgaccag	gtcacgcttc	gcggcttctc	caagccctcg	300
gacctcgtgg	gcgtcttctc	ctgcgtgggc	ggtgctgggg	cgcggcgcac	gcgcgtcatc	360
tacgtgcaca	acagccctgg	agcccacctg	cttccagaca	aggtcacaca	cactgtgaac	420
aaaggtgaca	ccgctgtact	ttctgcacgt	gtgcacaagg	agaagcagac	agacgtgatc	480
tggaagagca	acggatccta	cttctacacc	ctggactggc	atgaagccca	ggatgggcgg	540
ttcctgctgc	agctcccaaa	tgtgcagcca	ccatcgagcg	gcattctacag	tgccacttac	600
ctggaagcca	gccccctggg	cagcgcttc	tttcggctca	tcgtgcgggg	ttgtggggct	660
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cacgaccatg	acggcgaatg	tgtatgcccc	cctggcttca	ctggcaccgc	ctgtgaacag	780
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cagtgccagt	gtcagaatgg	tggcacttgt	gaccgggtca	gtggttgtgt	ctgccccctc	1020
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tcagaactgg	agttcaactt	agagacgatg	ccccggatca	actgtgcagc	tgcagggaac	1140
cccttccccg	tgcggggcag	catagagcta	cgcaagccag	acggcactgt	gctcctgtcc	1200
accaaggcca	ttgtggagcc	agagaagacc	acagctgagt	tcgaggtgcc	ccgcttggtt	1260
cttgccgaca	gtgggttctg	ggagtgcctg	gtgtccacat	ctggcggcca	agacagccgg	1320
cgcttcaagg	tcaatgtgaa	agtgcacccc	gtgcccctgg	ctgcacctcg	gctcctgacc	1380
aagcagagcc	gccagcttgt	ggtctccccg	ctgggtctcg	tctctgggga	tggaacctac	1440
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tccgagatcc	agctgacatg	gaagcaccgc	gaggctctgc	ctggggccaa	atccaagtac	2040
gttggtggagg	tgccaggtggc	tgggggtgca	ggagaccac	tgtggataga	cgtggacagg	2100

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cctgaggaga caagcaccat catccgtggc ctcaacgcc a gcacgcgcta cctcttccgc 2160  
 atgcggggcca gcattcaggg gctcgggggac tggagcaaca cagtagaaga gtccaccctg 2220  
 ggcaacggtg agagggcagg gccacagga cccccgggc tctgagcggg gag 2273

&lt;210&gt; 222

&lt;211&gt; 751

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 222

Met	Val	Trp	Arg	Val	Pro	Pro	Phe	Leu	Leu	Pro	Ile	Leu	Phe	Leu	Ala
1				5				10					15		
Ser	His	Val	Gly	Ala	Ala	Val	Asp	Leu	Thr	Leu	Leu	Ala	Asn	Leu	Arg
			20					25					30		
Leu	Thr	Asp	Pro	Gln	Arg	Phe	Phe	Leu	Thr	Cys	Val	Ser	Gly	Glu	Ala
		35					40					45			
Gly	Ala	Gly	Arg	Gly	Ser	Asp	Ala	Trp	Gly	Pro	Pro	Leu	Leu	Leu	Glu
	50					55				60					
Lys	Asp	Asp	Arg	Ile	Val	Arg	Thr	Pro	Pro	Gly	Pro	Pro	Leu	Arg	Leu
65				70						75				80	
Ala	Arg	Asn	Gly	Ser	His	Gln	Val	Thr	Leu	Arg	Gly	Phe	Ser	Lys	Pro
			85					90					95		
Ser	Asp	Leu	Val	Gly	Val	Phe	Ser	Cys	Val	Gly	Gly	Ala	Gly	Ala	Arg
			100					105				110			
Arg	Thr	Arg	Val	Ile	Tyr	Val	His	Asn	Ser	Pro	Gly	Ala	His	Leu	Leu
		115				120					125				
Pro	Asp	Lys	Val	Thr	His	Thr	Val	Asn	Lys	Gly	Asp	Thr	Ala	Val	Leu
	130					135				140					
Ser	Ala	Arg	Val	His	Lys	Glu	Lys	Gln	Thr	Asp	Val	Ile	Trp	Lys	Ser
145				150						155				160	
Asn	Gly	Ser	Tyr	Phe	Tyr	Thr	Leu	Asp	Trp	His	Glu	Ala	Gln	Asp	Gly
			165					170					175		
Arg	Phe	Leu	Leu	Gln	Leu	Pro	Asn	Val	Gln	Pro	Pro	Ser	Ser	Gly	Ile
		180					185					190			
Tyr	Ser	Ala	Thr	Tyr	Leu	Glu	Ala	Ser	Pro	Leu	Gly	Ser	Ala	Phe	Phe
	195						200				205				
Arg	Leu	Ile	Val	Arg	Gly	Cys	Gly	Ala	Gly	Arg	Trp	Gly	Pro	Gly	Cys
	210				215					220					
Thr	Lys	Glu	Cys	Pro	Gly	Cys	Leu	His	Gly	Gly	Val	Cys	His	Asp	His
225				230					235					240	
Asp	Gly	Glu	Cys	Val	Cys	Pro	Pro	Gly	Phe	Thr	Gly	Thr	Arg	Cys	Glu
			245						250				255		
Gln	Ala	Cys	Arg	Glu	Gly	Arg	Phe	Gly	Gln	Ser	Cys	Gln	Glu	Gln	Cys
		260						265					270		
Pro	Gly	Ile	Ser	Gly	Cys	Arg	Gly	Leu	Thr	Phe	Cys	Leu	Pro	Asp	Pro
	275						280					285			
Tyr	Gly	Cys	Ser	Cys	Gly	Ser	Gly	Trp	Arg	Gly	Ser	Gln	Cys	Gln	Glu
	290				295					300					
Ala	Cys	Ala	Pro	Gly	His	Phe	Gly	Ala	Asp	Cys	Arg	Leu	Gln	Cys	Gln
305				310						315				320	
Cys	Gln	Asn	Gly	Gly	Thr	Cys	Asp	Arg	Phe	Ser	Gly	Cys	Val	Cys	Pro
			325					330					335		
Ser	Gly	Trp	His	Gly	Val	His	Cys	Glu	Lys	Ser	Asp	Arg	Ile	Pro	Gln
		340						345					350		
Ile	Leu	Asn	Met	Ala	Ser	Glu	Leu	Glu	Phe	Asn	Leu	Glu	Thr	Met	Pro
	355						360					365			

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Arg Ile Asn Cys Ala Ala Ala Gly Asn Pro Phe Pro Val Arg Gly Ser
  370          375          380
Ile Glu Leu Arg Lys Pro Asp Gly Thr Val Leu Leu Ser Thr Lys Ala
385          390          395          400
Ile Val Glu Pro Glu Lys Thr Thr Ala Glu Phe Glu Val Pro Arg Leu
          405          410          415
Val Leu Ala Asp Ser Gly Phe Trp Glu Cys Arg Val Ser Thr Ser Gly
          420          425          430
Gly Gln Asp Ser Arg Arg Phe Lys Val Asn Val Lys Val Pro Pro Val
          435          440          445
Pro Leu Ala Ala Pro Arg Leu Leu Thr Lys Gln Ser Arg Gln Leu Val
          450          455          460
Val Ser Pro Leu Val Ser Phe Ser Gly Asp Gly Pro Ile Ser Thr Val
465          470          475          480
Arg Leu His Tyr Arg Pro Gln Asp Ser Thr Met Asp Trp Ser Thr Ile
          485          490          495
Val Val Asp Pro Ser Glu Asn Val Thr Leu Met Asn Leu Arg Pro Lys
          500          505          510
Thr Gly Tyr Ser Val Arg Val Gln Leu Ser Arg Pro Gly Glu Gly Gly
          515          520          525
Glu Gly Ala Trp Gly Pro Pro Thr Leu Met Thr Thr Asp Cys Pro Glu
          530          535          540
Pro Leu Leu Gln Pro Trp Leu Glu Gly Trp His Val Glu Gly Thr Asp
545          550          555          560
Arg Leu Arg Val Ser Trp Ser Leu Pro Leu Val Pro Gly Pro Leu Val
          565          570          575
Gly Asp Gly Phe Leu Leu Arg Leu Trp Asp Gly Thr Arg Gly Gln Glu
          580          585          590
Arg Arg Glu Asn Val Ser Ser Pro Gln Ala Arg Thr Ala Leu Leu Thr
          595          600          605
Gly Leu Thr Pro Gly Thr His Tyr Gln Leu Asp Val Gln Leu Tyr His
          610          615          620
Cys Thr Leu Leu Gly Pro Ala Ser Pro Pro Ala His Val Leu Leu Pro
625          630          635          640
Pro Ser Gly Pro Pro Ala Pro Arg His Leu His Ala Gln Ala Leu Ser
          645          650          655
Asp Ser Glu Ile Gln Leu Thr Trp Lys His Pro Glu Ala Leu Pro Gly
          660          665          670
Pro Ile Ser Lys Tyr Val Val Glu Val Gln Val Ala Gly Gly Ala Gly
          675          680          685
Asp Pro Leu Trp Ile Asp Val Asp Arg Pro Glu Glu Thr Ser Thr Ile
          690          695          700
Ile Arg Gly Leu Asn Ala Ser Thr Arg Tyr Leu Phe Arg Met Arg Ala
705          710          715          720
Ser Ile Gln Gly Leu Gly Asp Trp Ser Asn Thr Val Glu Glu Ser Thr
          725          730          735
Leu Gly Asn Gly Glu Arg Ala Gly Pro Thr Gly Pro Pro Gly Leu
          740          745          750

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&lt;210&gt; 223

&lt;211&gt; 2432

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 223



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catttcgccc ggctcgaggt gcaggatgca gagcaagggt ctgctggccg tcgccctgtg 60
gctctgcgtg gagacccggg ccgcctctgt gggtttgcct agtgtttctc ttgatctgcc 120
caggctcagc atacaaaaag acatacttac aattaagggt aatacaactc ttcaaattac 180
ttgcagggga cagagggact tggactggct ttggcccaat aatcagagtg gcagtgcgca 240
aaggggtggag gtgactgagt gcagcgatgg cctcttctgt aagacactca caattccaaa 300
agtgatcgga aatgacactg gagcctacaa gtgcttctac cgggaaactg acttggcctc 360
ggtcattttat gtctatgttc aagattacag atctccattt attgcttctg ttagtgacca 420
acatggagtc gtgtacatta ctgagaacaa aaacaaaact gtggtgattc catgtctcgg 480
gtccatttca aatctcaacg tgtcactttg tgcaagatac ccagaaaaga gatttgttcc 540
tgatggtaac agaatttcct gggacagcaa gaagggtctt actattccca gctacatgat 600
cagctatgct ggcatggctc tctgtgaagc aaaaattaat gatgaaagt accagtctat 660
tatgtacata gttgtcgttg tagggatatag gatttatgat gtggttctga gtccgtctca 720
tggaaattgaa ctatctgttg gagaaaagct tgtcttaaat tgtacagcaa gaactgaact 780
aaatgtgggg attgacttca actgggaata cccttcttcg aagcatcagc ataagaaact 840
tgtaaaccca gacctaataa cccagtctgg gactgagatg aagaaatttt tgagcacttt 900
aactatagat ggtgtaaccc ggagtgcaca aggattgtac acctgtgcag catccagtgg 960
gctgatgacc aagaagaaca gcacatttgt cagggtccat gaaaaacctt ttgttgcctt 1020
tggaaagtggc atggaatctc tgggtggaagc caggggtggg gagcgtgtca gaatccctgc 1080
gaagtacctt ggttaccac cccagaaat aaaaatggtat aaaaatggaa tacccttga 1140
gtccaatcac acaattaaag cggggcatgt actgacgatt atggaagtga gtgaaagaga 1200
cacaggaaat tacactgtca tccttaccaa tccatttca aaggagaagc agagccatgt 1260
ggtctctctg gttgtgtatg tcccacccca gattggtgag aaatctctaa tctctcctgt 1320
ggattcctac cagtacggca ccaactcaaac gctgacatgt acggtctatg ccattcctcc 1380
cccgcacac atccactggt attggcagtt ggaggaagag tgcgccaacg agcccagcca 1440
agctgtctca gtgacaaacc catacccttg tgaagaatgg agaagtgtgg aggacttcca 1500
gggagggaaat aaaattgaag ttaataaaaa tcaatttgct ctaattgaag gaaaaaacia 1560
aactgtaagt acccttggtt tccaagcggc aaatgtgtca gctttgtaca aatgtgaagc 1620
ggtcaacaaa gtcgggagag gagagagggt gatctccttc cacgtgacca ggggtcctga 1680
aattactttg caacctgaca tgcagccac tgagcaggag agcgtgtctt tgtggtgcac 1740
tgcagacaga tctacgtttg agaacctcac atggtacaag cttggcccac agcctctgcc 1800
aatccatgtg ggagagttgc ccacacctgt ttgcaagaac ttggatactc tttggaaatt 1860
gaatgccacc atgttctcta atagcacaaa tgacattttg atcatggagc ttaagaatgc 1920
atccttgacg gaccaaggag actatgtctg ccttgctcaa gacaggaaga ccaagaaaag 1980
acattgcgtg gtcaggcagc tcacagtcct agagcgtgtg gcacccacga tcacagggaa 2040
cctggagaat cagacgacaa gtattgggga aagcatcgaa gtctcatgca cggcatctgg 2100
gaatccccct ccacagatca tgtggtttaa agataatgag acccttgtag aagactcaga 2160
gtgaggaagg aggacgaagg cctctacacc tgccaggcat gcagtgttct tggctgtgca 2220
aaagtggagg catttttcat aatagaagggt gcccaggaaa agacgaactt ggaaatcatt 2280
attctagtag gcacggcggt gattgccaatg ttcttctggc tacttcttgt catcatccta 2340
cggaccgtta agcgggcca tggaggggaa ctgaagacag gctacttgtc catcgtcatg 2400
gatccagatg aactccatt ggatgaacat tg 2432

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&lt;210&gt; 224

&lt;211&gt; 712

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 224

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Met Gln Ser Lys Val Leu Leu Ala Val Ala Leu Trp Leu Cys Val Glu
1           5           10           15
Thr Arg Ala Ala Ser Val Gly Leu Pro Ser Val Ser Leu Asp Leu Pro
20           25           30
Arg Leu Ser Ile Gln Lys Asp Ile Leu Thr Ile Lys Ala Asn Thr Thr
35           40           45
Leu Gln Ile Thr Cys Arg Gly Gln Arg Asp Leu Asp Trp Leu Trp Pro
50           55           60

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Asn	Asn	Gln	Ser	Gly	Ser	Glu	Gln	Arg	Val	Glu	Val	Thr	Glu	Cys	Ser	65	70	75	80
Asp	Gly	Leu	Phe	Cys	Lys	Thr	Leu	Thr	Ile	Pro	Lys	Val	Ile	Gly	Asn				
				85					90					95					
Asp	Thr	Gly	Ala	Tyr	Lys	Cys	Phe	Tyr	Arg	Glu	Thr	Asp	Leu	Ala	Ser				
			100					105					110						
Val	Ile	Tyr	Val	Tyr	Val	Gln	Asp	Tyr	Arg	Ser	Pro	Phe	Ile	Ala	Ser				
		115					120					125							
Val	Ser	Asp	Gln	His	Gly	Val	Val	Tyr	Ile	Thr	Glu	Asn	Lys	Asn	Lys				
	130					135					140								
Thr	Val	Val	Ile	Pro	Cys	Leu	Gly	Ser	Ile	Ser	Asn	Leu	Asn	Val	Ser				
	145				150					155					160				
Leu	Cys	Ala	Arg	Tyr	Pro	Glu	Lys	Arg	Phe	Val	Pro	Asp	Gly	Asn	Arg				
			165						170					175					
Ile	Ser	Trp	Asp	Ser	Lys	Lys	Gly	Phe	Thr	Ile	Pro	Ser	Tyr	Met	Ile				
		180						185					190						
Ser	Tyr	Ala	Gly	Met	Val	Phe	Cys	Glu	Ala	Lys	Ile	Asn	Asp	Glu	Ser				
	195						200					205							
Tyr	Gln	Ser	Ile	Met	Tyr	Ile	Val	Val	Val	Val	Gly	Tyr	Arg	Ile	Tyr				
	210					215					220								
Asp	Val	Val	Leu	Ser	Pro	Ser	His	Gly	Ile	Glu	Leu	Ser	Val	Gly	Glu				
	225				230					235					240				
Lys	Leu	Val	Leu	Asn	Cys	Thr	Ala	Arg	Thr	Glu	Leu	Asn	Val	Gly	Ile				
			245						250					255					
Asp	Phe	Asn	Trp	Glu	Tyr	Pro	Ser	Ser	Lys	His	Gln	His	Lys	Lys	Leu				
		260						265					270						
Val	Asn	Arg	Asp	Leu	Lys	Thr	Gln	Ser	Gly	Ser	Glu	Met	Lys	Lys	Phe				
	275						280					285							
Leu	Ser	Thr	Leu	Thr	Ile	Asp	Gly	Val	Thr	Arg	Ser	Asp	Gln	Gly	Leu				
	290					295					300								
Tyr	Thr	Cys	Ala	Ala	Ser	Ser	Gly	Leu	Met	Thr	Lys	Lys	Asn	Ser	Thr				
	305				310					315					320				
Phe	Val	Arg	Val	His	Glu	Lys	Pro	Phe	Val	Ala	Phe	Gly	Ser	Gly	Met				
			325						330					335					
Glu	Ser	Leu	Val	Glu	Ala	Thr	Val	Gly	Glu	Arg	Val	Arg	Ile	Pro	Ala				
		340						345					350						
Lys	Tyr	Leu	Gly	Tyr	Pro	Pro	Pro	Glu	Ile	Lys	Trp	Tyr	Lys	Asn	Gly				
	355						360					365							
Ile	Pro	Leu	Glu	Ser	Asn	His	Thr	Ile	Lys	Ala	Gly	His	Val	Leu	Thr				
	370				375						380								
Ile	Met	Glu	Val	Ser	Glu	Arg	Asp	Thr	Gly	Asn	Tyr	Thr	Val	Ile	Leu				
	385				390					395					400				
Thr	Asn	Pro	Ile	Ser	Lys	Glu	Lys	Gln	Ser	His	Val	Val	Ser	Leu	Val				
			405						410					415					
Val	Tyr	Val	Pro	Pro	Gln	Ile	Gly	Glu	Lys	Ser	Leu	Ile	Ser	Pro	Val				
		420						425					430						
Asp	Ser	Tyr	Gln	Tyr	Gly	Thr	Thr	Gln	Thr	Leu	Thr	Cys	Thr	Val	Tyr				
	435						440					445							
Ala	Ile	Pro	Pro	Pro	His	His	Ile	His	Trp	Tyr	Trp	Gln	Leu	Glu	Glu				
	450					455					460								
Glu	Cys	Ala	Asn	Glu	Pro	Ser	Gln	Ala	Val	Ser	Val	Thr	Asn	Pro	Tyr				
	465				470					475					480				
Pro	Cys	Glu	Glu	Trp	Arg	Ser	Val	Glu	Asp	Phe	Gln	Gly	Gly	Asn	Lys				
			485						490					495					
Ile	Glu	Val	Asn	Lys	Asn	Gln	Phe	Ala	Leu	Ile	Glu	Gly	Lys	Asn	Lys				
			500					505					510						

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Thr Val Ser Thr Leu Val Ile Gln Ala Ala Asn Val Ser Ala Leu Tyr  
           515                          520                          525  
 Lys Cys Glu Ala Val Asn Lys Val Gly Arg Gly Glu Arg Val Ile Ser  
           530                          535                          540  
 Phe His Val Thr Arg Gly Pro Glu Ile Thr Leu Gln Pro Asp Met Gln  
 545                          550                          555                          560  
 Pro Thr Glu Gln Glu Ser Val Ser Leu Trp Cys Thr Ala Asp Arg Ser  
                           565                          570                          575  
 Thr Phe Glu Asn Leu Thr Trp Tyr Lys Leu Gly Pro Gln Pro Leu Pro  
                           580                          585                          590  
 Ile His Val Gly Glu Leu Pro Thr Pro Val Cys Lys Asn Leu Asp Thr  
                           595                          600                          605  
 Leu Trp Lys Leu Asn Ala Thr Met Phe Ser Asn Ser Thr Asn Asp Ile  
           610                          615                          620  
 Leu Ile Met Glu Leu Lys Asn Ala Ser Leu Gln Asp Gln Gly Asp Tyr  
 625                          630                          635                          640  
 Val Cys Leu Ala Gln Asp Arg Lys Thr Lys Lys Arg His Cys Val Val  
                           645                          650                          655  
 Arg Gln Leu Thr Val Leu Glu Arg Val Ala Pro Thr Ile Thr Gly Asn  
                           660                          665                          670  
 Leu Glu Asn Gln Thr Thr Ser Ile Gly Glu Ser Ile Glu Val Ser Cys  
                           675                          680                          685  
 Thr Ala Ser Gly Asn Pro Pro Pro Gln Ile Met Trp Phe Lys Asp Asn  
           690                          695                          700  
 Glu Thr Leu Val Glu Asp Ser Glu  
 705                          710

&lt;210&gt; 225

&lt;211&gt; 2620

&lt;212&gt; DNA

&lt;213&gt; Homo Sapiens

&lt;400&gt; 225

gcagcggccg gagatgcagc ggggcgccgc gctgtgcctg cgactgtggc tctgcctggg 60  
 actcctggac ggcctggtga gtggctactc catgaccccc ccgaccttga acatcacgga 120  
 ggagtcacac gtcacgcaca ccggtgacag cctgtccatc tctgcagggg gacagcacc 180  
 cctcgagtgg gcttgccag gagctcagga ggcgccagcc accggagaca aggacagcga 240  
 ggacacgggg gtggtgcgag actgcgaggg cacagacgcc aggccctact gcaaggtgtt 300  
 gctgctgcac gaggtacatg ccaacgacac aggcagctac gtctgctact acaagtacat 360  
 caaggcacgc atcgagggca ccacggccgc cagctcctac gtgttcgtga gagactttga 420  
 gcagccattc atcaacaagc ctgacacgct cttggtcaac aggaaggacg ccatgtgggt 480  
 gccctgtctg gtgtccatcc ccggcctcaa tgtcacgctg cgctcgcaaa gctcgggtgt 540  
 gtggccagac gggcaggagg tgggtgtgga tgaccggcgg ggcattgctg tgtccacgcc 600  
 actgctgcac gatgccctgt acctgcagtg cgagaccacc tggggagacc aggacttcct 660  
 ttccaacccc ttcttggtgc acatcacagg caacgagctc tatgacatcc agctgttgcc 720  
 caggaagtcg ctggagctgc tggtagggga gaagctggtc ctgaactgca ccgtgtgggc 780  
 tgagtttaac tcaggtgtca cctttgactg ggactaccca gggaagcagg cagagcgggg 840  
 taagtgggtg cccgagcgac gctcccagca gaccacaca gaactctcca gcatcctgac 900  
 catccacaac gtcagccagc acgacctggg ctcgatatgt tgcaaggcca acaacggcat 960  
 ccagcgattt cgggagagca ccgaggtcat tgtgcatgaa aatcccttca tcagcgtcga 1020  
 gtggctcaaa ggacctatcc tggaggccac ggcaggagac gagctggtga agctgcccgt 1080  
 gaagctggca gcgtaccccc cgcccaggtt ccagtggtag aaggatggaa aggcactgtc 1140  
 cggcgccac agtccacatg ccctgggtgt caaggaggtg acagaggcca gcacaggcac 1200  
 ctacacccct gccctgtgga actccgctgc tggcctgagg cgcaacatca gcctggagct 1260  
 ggtggtgaat gtgccccccc agatacatga gaaggaggcc tcctcccca gcatctactc 1320

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gcgtcacagc cgccaggccc tcacctgcac ggcctacggg gtgcccctgc ctctcagcat 1380
ccagtggcac tggcggccct ggacaccctg caagatgttt gccacgcgta gtctccggcg 1440
gcggcagcag caagacctca tgccacagtg ccgtgactgg agggcgggtga ccacgcagga 1500
tgccgtgaac cccatcgaga gcctggacac ctggaccgag tttgtggagg gaaagaataa 1560
gactgtgagc aagctgggtga tccagaatgc caacgtgtct gccatgtaca agtgtgtggt 1620
ctccaacaag gtgggcccagg atgagcggct catctacttc tatgtgacca ccatccccga 1680
cggcttcacc atcgaatcca agccatccga ggagctacta gagggccagc cgggtgctcct 1740
gagctgccaa gccgacagct acaagtacga gcatctgcgc tggtaaccgc tcaacctgtc 1800
cacgctgcac gatgcgcacg ggaaccgct tctgctcgac tgcaagaacg tgcctctgtt 1860
cgccacccct ctggccgcca gcctggagga ggtggcacct ggggcgcgcc acgccacgct 1920
cagcctgagt atcccccgcg tcgcgcccga gcacgagggc cactatgtgt gcgaagtgc 1980
agaccggcgc agccatgaca agcactgcca caagaagtac ctgtcggtgc aggccttgg 2040
agccctcgcg ctacgcgaga acttgaccga cctcctgggtg aacgtgagcg actcgctgga 2100
gatgcagtgc ttggtggccg gagcgacgc gccacgcatc gtgtggtaca aagacgagag 2160
gctgctggag gaaaagtctg gtaggagggg tggccctggc gaagggcagg tccggaggcc 2220
cgcgaggccg acgatcccaa acccaggtgg acccgacact ccacccacc ccctgcagga 2280
gtcgacttgg cggactccaa ccagaagctg agcatccagc gcgtgcgcga ggaggtgagc 2340
ggacgctatc tgtgcagcgt gtgcaacgcc aagggtgcg tcaactcctc cgccagcggtg 2400
gccgtggaag gctccgagga taagggcagc atggagatcg tgatccttgt cggtaaccggc 2460
gtcatcgctg tcttcttctg ggtcctcctc ctctcatct tctgtaacat gaggaggccg 2520
gcccacgcag acatcaagac gggctacctg tccatcatca tggaccccg ggaggtgcct 2580
ctggaggagc aatgcgaata cctgtcctac gatgccagcc 2620

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&lt;210&gt; 226

&lt;211&gt; 765

&lt;212&gt; PRT

&lt;213&gt; Homo Sapiens

&lt;400&gt; 226

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Met Gln Arg Gly Ala Ala Leu Cys Leu Arg Leu Trp Leu Cys Leu Gly
 1          5          10          15
Leu Leu Asp Gly Leu Val Ser Gly Tyr Ser Met Thr Pro Pro Thr Leu
 20          25          30
Asn Ile Thr Glu Glu Ser His Val Ile Asp Thr Gly Asp Ser Leu Ser
 35          40          45
Ile Ser Cys Arg Gly Gln His Pro Leu Glu Trp Ala Trp Pro Gly Ala
 50          55          60
Gln Glu Ala Pro Ala Thr Gly Asp Lys Asp Ser Glu Asp Thr Gly Val
 65          70          75
Val Arg Asp Cys Glu Gly Thr Asp Ala Arg Pro Tyr Cys Lys Val Leu
 85          90          95
Leu Leu His Glu Val His Ala Asn Asp Thr Gly Ser Tyr Val Cys Tyr
100          105          110
Tyr Lys Tyr Ile Lys Ala Arg Ile Glu Gly Thr Thr Ala Ala Ser Ser
115          120          125
Tyr Val Phe Val Arg Asp Phe Glu Gln Pro Phe Ile Asn Lys Pro Asp
130          135          140
Thr Leu Leu Val Asn Arg Lys Asp Ala Met Trp Val Pro Cys Leu Val
145          150          155
Ser Ile Pro Gly Leu Asn Val Thr Leu Arg Ser Gln Ser Ser Val Leu
165          170          175
Trp Pro Asp Gly Gln Glu Val Val Trp Asp Asp Arg Arg Gly Met Leu
180          185          190
Val Ser Thr Pro Leu Leu His Asp Ala Leu Tyr Leu Gln Cys Glu Thr
195          200          205
Thr Trp Gly Asp Gln Asp Phe Leu Ser Asn Pro Phe Leu Val His Ile

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210						215						220					
Thr	Gly	Asn	Glu	Leu	Tyr	Asp	Ile	Gln	Leu	Leu	Pro	Arg	Lys	Ser	Leu		
225					230					235					240		
Glu	Leu	Leu	Val	Gly	Glu	Lys	Leu	Val	Leu	Asn	Cys	Thr	Val	Trp	Ala		
				245					250					255			
Glu	Phe	Asn	Ser	Gly	Val	Thr	Phe	Asp	Trp	Asp	Tyr	Pro	Gly	Lys	Gln		
			260					265					270				
Ala	Glu	Arg	Gly	Lys	Trp	Val	Pro	Glu	Arg	Arg	Ser	Gln	Gln	Thr	His		
		275					280					285					
Thr	Glu	Leu	Ser	Ser	Ile	Leu	Thr	Ile	His	Asn	Val	Ser	Gln	His	Asp		
		290				295					300						
Leu	Gly	Ser	Tyr	Val	Cys	Lys	Ala	Asn	Asn	Gly	Ile	Gln	Arg	Phe	Arg		
305					310					315					320		
Glu	Ser	Thr	Glu	Val	Ile	Val	His	Glu	Asn	Pro	Phe	Ile	Ser	Val	Glu		
			325						330					335			
Trp	Leu	Lys	Gly	Pro	Ile	Leu	Glu	Ala	Thr	Ala	Gly	Asp	Glu	Leu	Val		
			340					345					350				
Lys	Leu	Pro	Val	Lys	Leu	Ala	Ala	Tyr	Pro	Pro	Pro	Glu	Phe	Gln	Trp		
		355				360						365					
Tyr	Lys	Asp	Gly	Lys	Ala	Leu	Ser	Gly	Arg	His	Ser	Pro	His	Ala	Leu		
		370				375					380						
Val	Leu	Lys	Glu	Val	Thr	Glu	Ala	Ser	Thr	Gly	Thr	Tyr	Thr	Leu	Ala		
385					390					395					400		
Leu	Trp	Asn	Ser	Ala	Ala	Gly	Leu	Arg	Arg	Asn	Ile	Ser	Leu	Glu	Leu		
			405						410					415			
Val	Val	Asn	Val	Pro	Pro	Gln	Ile	His	Glu	Lys	Glu	Ala	Ser	Ser	Pro		
		420						425					430				
Ser	Ile	Tyr	Ser	Arg	His	Ser	Arg	Gln	Ala	Leu	Thr	Cys	Thr	Ala	Tyr		
		435				440						445					
Gly	Val	Pro	Leu	Pro	Leu	Ser	Ile	Gln	Trp	His	Trp	Arg	Pro	Trp	Thr		
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&lt;309&gt; 2004-11-16

&lt;400&gt; 230

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- 195 -

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&lt;213&gt; Homo sapiens

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&lt;308&gt; GenBank No. L36644

&lt;309&gt; 1995-08-10

&lt;400&gt; 232

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- 198 -

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. AL133666

&lt;309&gt; 2005-01-20

&lt;400&gt; 233

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&lt;308&gt; GenBank No. NM004440

&lt;309&gt; 2005-01-26

&lt;400&gt; 234

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&lt;308&gt; GenBank No. NM020526

&lt;309&gt; 2004-11-16

&lt;400&gt; 235

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&lt;210&gt; 241

&lt;211&gt; 5511

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. NM001982

&lt;309&gt; 2004-12-20

&lt;400&gt; 241

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&lt;211&gt; 4587

&lt;212&gt; DNA

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&lt;308&gt; GenBank No. NM000141

&lt;309&gt; 2004-12-20

&lt;400&gt; 242

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&lt;211&gt; 4093

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

- 213 -

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&lt;308&gt; GenBank No. NM000142

&lt;309&gt; 2004-12-20

&lt;400&gt; 243

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&lt;210&gt; 249

&lt;211&gt; 972

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. NP005202



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&lt;309&gt; 2004-10-26

&lt;400&gt; 249

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Glu Trp Asp Gly Pro Pro Ser Pro His Trp Thr Leu Tyr Ser Asp Gly
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Ser Ser Ser Ile Leu Ser Thr Asn Asn Ala Thr Phe Gln Asn Thr Gly
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Thr Tyr Arg Cys Thr Glu Pro Gly Asp Pro Leu Gly Gly Ser Ala Ala
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Ile His Leu Tyr Val Lys Asp Pro Ala Arg Pro Trp Asn Val Leu Ala
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Gln Glu Val Val Val Phe Glu Asp Gln Asp Ala Leu Leu Pro Cys Leu
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Gly Arg Pro Leu Met Arg His Thr Asn Tyr Ser Phe Ser Pro Trp His
 145      150      155      160
Gly Phe Thr Ile His Arg Ala Lys Phe Ile Gln Ser Gln Asp Tyr Gln
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Cys Ser Ala Leu Met Gly Gly Arg Lys Val Met Ser Ile Ser Ile Arg
 180      185      190
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 195      200      205
Pro Ala Glu Leu Val Arg Ile Arg Gly Glu Ala Ala Gln Ile Val Cys
 210      215      220
Ser Ala Ser Ser Val Asp Val Asn Phe Asp Val Phe Leu Gln His Asn
 225      230      235      240
Asn Thr Lys Leu Ala Ile Pro Gln Gln Ser Asp Phe His Asn Asn Arg
 245      250      255
Tyr Gln Lys Val Leu Thr Leu Asn Leu Asp Gln Val Asp Phe Gln His
 260      265      270
Ala Gly Asn Tyr Ser Cys Val Ala Ser Asn Val Gln Gly Lys His Ser
 275      280      285
Thr Ser Met Phe Phe Arg Val Val Glu Ser Ala Tyr Leu Asn Leu Ser
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Ser Glu Gln Asn Leu Ile Gln Glu Val Thr Val Gly Glu Gly Leu Asn
 305      310      315      320
Leu Lys Val Met Val Glu Ala Tyr Pro Gly Leu Gln Gly Phe Asn Trp
 325      330      335
Thr Tyr Leu Gly Pro Phe Ser Asp His Gln Pro Glu Pro Lys Leu Ala
 340      345      350
Asn Ala Thr Thr Lys Asp Thr Tyr Arg His Thr Phe Thr Leu Ser Leu
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Pro Arg Leu Lys Pro Ser Glu Ala Gly Arg Tyr Ser Phe Leu Ala Arg
 370      375      380
Asn Pro Gly Gly Trp Arg Ala Leu Thr Phe Glu Leu Thr Leu Arg Tyr
 385      390      395      400
Pro Pro Glu Val Ser Val Ile Trp Thr Phe Ile Asn Gly Ser Gly Thr
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Leu Leu Cys Ala Ala Ser Gly Tyr Pro Gln Pro Asn Val Thr Trp Leu

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Val	Trp	Asp	Asp	Pro	Tyr	Pro	Glu	Val	Leu	Ser	Gln	Glu	Pro	Phe	His					
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Lys	Val	Thr	Val	Gln	Ser	Leu	Leu	Thr	Val	Glu	Thr	Leu	Glu	His	Asn					
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Gln	Thr	Tyr	Glu	Cys	Arg	Ala	His	Asn	Ser	Val	Gly	Ser	Gly	Ser	Trp					
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Phe	Leu	Phe	Thr	Pro	Val	Val	Val	Ala	Cys	Met	Ser	Ile	Met	Ala	Leu					
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Lys	Tyr	Gln	Val	Arg	Trp	Lys	Ile	Ile	Glu	Ser	Tyr	Glu	Gly	Asn	Ser					
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Tyr	Thr	Phe	Ile	Asp	Pro	Thr	Gln	Leu	Pro	Tyr	Asn	Glu	Lys	Trp	Glu					
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Phe	Gly	Lys	Val	Val	Glu	Ala	Thr	Ala	Phe	Gly	Leu	Gly	Lys	Glu	Asp					
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Asn	Phe	Leu	Arg	Arg	Lys	Ala	Glu	Ala	Met	Leu	Gly	Pro	Ser	Leu	Ser					
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Asp	Thr	Tyr	Val	Glu	Met	Arg	Pro	Val	Ser	Thr	Ser	Ser	Asn	Asp	Ser					
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Phe	Ser	Glu	Gln	Asp	Leu	Asp	Lys	Glu	Asp	Gly	Arg	Pro	Leu	Glu	Leu					
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Thr	Val	Gln	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Ile	Leu	Leu	Trp	Glu	Ile					
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Phe	Ser	Leu	Gly	Leu	Asn	Pro	Tyr	Pro	Gly	Ile	Leu	Val	Asn	Ser	Lys					
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Ala	Pro	Lys	Asn	Ile	Tyr	Ser	Ile	Met	Gln	Ala	Cys	Trp	Ala	Leu
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Gln	Ala	Gln	Glu	Asp	Arg	Arg	Glu	Arg	Asp	Tyr	Thr	Asn	Leu	Pro
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Ser	Ser	Arg	Ser	Gly	Gly	Ser	Gly	Ser	Ser	Ser	Ser	Glu	Leu	Glu
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Glu	Ser	Ser	Ser	Glu	His	Leu	Thr	Cys	Cys	Glu	Gln	Gly	Asp	Ile
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 <212> PRT  
 <213> Homo sapiens

<300>  
 <308> GenBank No. NP054699  
 <309> 2004-10-26

<400> 250

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Glu	Ser	Ser	Asp	Gly	Asp	Gly	Ala	Trp	Cys	Pro	Ala	Gly	Ser	Val
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Pro	Lys	Glu	Glu	Glu	Tyr	Leu	Gln	Val	Asp	Leu	Gln	Arg	Leu	His
			85					90					95	
Val	Ala	Leu	Val	Gly	Thr	Gln	Gly	Arg	His	Ala	Gly	Gly	Leu	Gly
	100						105						110	
Glu	Phe	Ser	Arg	Ser	Tyr	Arg	Leu	Arg	Tyr	Ser	Arg	Asp	Gly	Arg
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Trp	Met	Gly	Trp	Lys	Asp	Arg	Trp	Gly	Gln	Glu	Val	Ile	Ser	Gly
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Glu	Asp	Pro	Glu	Gly	Val	Val	Leu	Lys	Asp	Leu	Gly	Pro	Pro	Met
145				150					155					160
Ala	Arg	Leu	Val	Arg	Phe	Tyr	Pro	Arg	Ala	Asp	Arg	Val	Met	Ser
			165					170					175	
Cys	Leu	Arg	Val	Glu	Leu	Tyr	Gly	Cys	Leu	Trp	Arg	Asp	Gly	Leu
	180						185					190		
Ser	Tyr	Thr	Ala	Pro	Val	Gly	Gln	Thr	Met	Tyr	Leu	Ser	Glu	Ala
	195					200					205			
Tyr	Leu	Asn	Asp	Ser	Thr	Tyr	Asp	Gly	His	Thr	Val	Gly	Gly	Leu
	210				215						220			
Tyr	Gly	Gly	Leu	Gly	Gln	Leu	Ala	Asp	Gly	Val	Val	Gly	Leu	Asp
225				230					235					240
Phe	Arg	Lys	Ser	Gln	Glu	Leu	Arg	Val	Trp	Pro	Gly	Tyr	Asp	Tyr

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Gly	Trp	Ser	Asn	His	Ser	Phe	Ser	Ser	Gly	Tyr	Val	Glu	Met	Glu	Phe		
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		275					280					285					
Asn	Met	His	Thr	Leu	Gly	Ala	Arg	Leu	Pro	Gly	Gly	Val	Glu	Cys	Arg		
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Phe	Arg	Arg	Gly	Pro	Ala	Met	Ala	Trp	Glu	Gly	Glu	Pro	Met	Arg	His		
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Asn	Leu	Gly	Gly	Asn	Leu	Gly	Asp	Pro	Arg	Ala	Arg	Ala	Val	Ser	Val		
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Pro	Leu	Gly	Gly	Arg	Val	Ala	Arg	Phe	Leu	Gln	Cys	Arg	Phe	Leu	Phe		
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Trp	Trp	Pro	Pro	Gly	Pro	Pro	Pro	Thr	Asn	Phe	Ser	Ser	Leu	Glu	Leu		
385				390					395						400		
Glu	Pro	Arg	Gly	Gln	Gln	Pro	Val	Ala	Lys	Ala	Glu	Gly	Ser	Pro	Thr		
			405					410						415			
Ala	Ile	Leu	Ile	Gly	Cys	Leu	Val	Ala	Ile	Ile	Leu	Leu	Leu	Leu	Leu		
			420					425					430				
Ile	Ile	Ala	Leu	Met	Leu	Trp	Arg	Leu	His	Trp	Arg	Arg	Leu	Leu	Ser		
		435					440					445					
Lys	Ala	Glu	Arg	Arg	Val	Leu	Glu	Glu	Glu	Leu	Thr	Val	His	Leu	Ser		
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Val	Pro	Gly	Asp	Thr	Ile	Leu	Ile	Asn	Asn	Arg	Pro	Gly	Pro	Arg	Glu		
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Pro	Pro	Pro	Tyr	Gln	Glu	Pro	Arg	Pro	Arg	Gly	Asn	Pro	Pro	His	Ser		
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Ala	Pro	Cys	Val	Pro	Asn	Gly	Ser	Ala	Leu	Leu	Leu	Ser	Asn	Pro	Ala		
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Tyr	Arg	Leu	Leu	Leu	Ala	Thr	Tyr	Ala	Arg	Pro	Pro	Arg	Gly	Pro	Gly		
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Pro	Pro	Thr	Pro	Ala	Trp	Ala	Lys	Pro	Thr	Asn	Thr	Gln	Ala	Tyr	Ser		
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Leu	Gln	Gly	Val	Thr	Gly	Gly	Asn	Thr	Tyr	Ala	Val	Pro	Ala	Leu	Pro		
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Pro	Gly	Ala	Val</														

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690		695		700
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705		710		715
Lys Ala Ala Glu Gly Ala Pro Gly Asp Gly Gln Ala Ala Gln Gly Pro				
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Thr Ile Ser Tyr Pro Met Leu Leu His Val Ala Ala Gln Ile Ala Ser				
	740		745	750
Gly Met Arg Tyr Leu Ala Thr Leu Asn Phe Val His Arg Asp Leu Ala				
	755		760	765
Thr Arg Asn Cys Leu Val Gly Glu Asn Phe Thr Ile Lys Ile Ala Asp				
	770		775	780
Phe Gly Met Ser Arg Asn Leu Tyr Ala Gly Asp Tyr Tyr Arg Val Gln				
785		790		795
Gly Arg Ala Val Leu Pro Ile Arg Trp Met Ala Trp Glu Cys Ile Leu				
	805		810	815
Met Gly Lys Phe Thr Thr Ala Ser Asp Val Trp Ala Phe Gly Val Thr				
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Leu Trp Glu Val Leu Met Leu Cys Arg Ala Gln Pro Phe Gly Ser Ala				
	835		840	845
His Arg Arg Ala Gly His Arg Glu Arg Gly Gly Val Leu Pro Gly Pro				
	850		855	860
Gly Pro Ala Val Tyr Leu Ser Arg Pro Pro Ala Cys Pro Gln Gly Leu				
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Tyr Glu Leu Met Leu Arg Cys Trp Ser Arg Glu Ser Glu Gln Arg Pro				
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 <309> 2004-10-26

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 Pro Leu Gly Met Ser Gly Gly Gln Ile Pro Asp Glu Asp Ile Thr Ala  
 35 40 45  
 Ser Ser Gln Trp Ser Glu Ser Thr Ala Ala Lys Tyr Gly Arg Leu Asp  
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 Ser Glu Glu Gly Asp Gly Ala Trp Cys Pro Glu Ile Pro Val Glu Pro  
 65 70 75 80  
 Asp Asp Leu Lys Glu Phe Leu Gln Ile Asp Leu His Thr Leu His Phe  
 85 90 95  
 Ile Thr Leu Val Gly Thr Gln Gly Arg His Ala Gly Gly His Gly Ile  
 100 105 110  
 Glu Phe Ala Pro Met Tyr Lys Ile Asn Tyr Ser Arg Asp Gly Thr Arg

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Cys	Met	Arg	Val	Glu	Leu	Tyr	Gly	Cys	Val	Trp	Leu	Asp	Gly	Leu	Val			
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Ile	Ile	Tyr	Leu	Asn	Asp	Ser	Val	Tyr	Asp	Gly	Ala	Val	Gly	Tyr	Ser			
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Met	Thr	Glu	Gly	Leu	Gly	Gln	Leu	Thr	Asp	Gly	Val	Ser	Gly	Leu	Asp			
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Tyr	Phe	Arg	Ser	Glu	Ala	Ser	Glu	Trp	Glu	Pro	Asn	Ala	Ile	Ser	Phe			
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Ser	Arg	Arg	Met	Leu	Asp	Asp	Glu	Met	Thr	Val	Ser	Leu	Ser	Leu	Pro			
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Ser	Asp	Ser	Ser	Met	Phe	Asn	Asn	Asn	Arg	Ser	Ser	Ser	Pro	Ser	Glu			
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<309> 2004-01-26

<400> 252																
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Gly	Thr	Ser	Asn	Lys	Leu	Thr	Gln	Leu	Gly	Thr	Phe	Glu	Asp	His	Phe	
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Leu	Ser	Leu	Gln	Arg	Met	Phe	Asn	Asn	Cys	Glu	Val	Val	Leu	Gly	Asn	

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50	55	60
Leu Glu Ile Thr Tyr Val	Gln Arg Asn Tyr Asp	Leu Ser Phe Leu Lys
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Thr Ile Gln Glu Val Ala	Gly Tyr Val Leu Ile Ala	Leu Asn Thr Val
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Glu Arg Ile Pro Leu Glu	Asn Leu Gln Ile Ile	Arg Gly Asn Met Tyr
	100	105
Tyr Glu Asn Ser Tyr Ala	Leu Ala Val Leu Ser	Asn Tyr Asp Ala Asn
	115	120
Lys Thr Gly Leu Lys Glu	Leu Pro Met Arg Asn	Leu Gln Glu Ile Leu
	130	135
His Gly Ala Val Arg Phe	Ser Asn Asn Pro Ala	Leu Cys Asn Val Glu
145	150	155
Ser Ile Gln Trp Arg Asp	Ile Val Ser Ser Asp	Phe Leu Ser Asn Met
	165	170
Ser Met Asp Phe Gln Asn	His Leu Gly Ser Cys	Gln Lys Cys Asp Pro
	180	185
Ser Cys Pro Asn Gly Ser	Cys Trp Gly Ala Gly	Glu Glu Asn Cys Gln
	195	200
Lys Leu Thr Lys Ile Ile	Cys Ala Gln Gln Cys	Ser Gly Arg Cys Arg
	210	215
Gly Lys Ser Pro Ser Asp	Cys Cys His Asn Gln	Cys Ala Ala Gly Cys
225	230	235
Thr Gly Pro Arg Glu Ser	Asp Cys Leu Val Cys	Arg Lys Phe Arg Asp
	245	250
Glu Ala Thr Cys Lys Asp	Thr Cys Pro Pro Leu	Met Leu Tyr Asn Pro
	260	265
Thr Thr Tyr Gln Met Asp	Val Asn Pro Glu Gly	Lys Tyr Ser Phe Gly
	275	280
Ala Thr Cys Val Lys Lys	Cys Pro Arg Asn Tyr	Val Val Thr Asp His
	290	295
Gly Ser Cys Val Arg Ala	Cys Gly Ala Asp Ser	Tyr Glu Met Glu Glu
305	310	315
Asp Gly Val Arg Lys Cys	Lys Lys Cys Glu Gly	Pro Cys Arg Lys Val
	325	330
Cys Asn Gly Ile Gly Ile	Gly Glu Phe Lys Asp	Ser Leu Ser Ile Asn
	340	345
Ala Thr Asn Ile Lys His	Phe Lys Asn Cys Thr	Ser Ile Ser Gly Asp
	355	360
Leu His Ile Leu Pro Val	Ala Phe Arg Gly Asp	Ser Phe Thr His Thr
	370	375
Pro Pro Leu Asp Pro Gln	Glu Leu Asp Ile Leu	Lys Thr Val Lys Glu
385	390	395
Ile Thr Gly Phe Leu Leu	Ile Gln Ala Trp Pro	Glu Asn Arg Thr Asp
	405	410
Leu His Ala Phe Glu Asn	Leu Glu Ile Ile Arg	Gly Arg Thr Lys Gln
	420	425
His Gly Gln Phe Ser Leu	Ala Val Ser Leu Asn	Ile Thr Ser Leu
	435	440
Gly Leu Arg Ser Leu Lys	Glu Ile Ser Asp Gly	Asp Val Ile Ile Ser
	450	455
Gly Asn Lys Asn Leu Cys	Tyr Ala Asn Thr Ile	Asn Trp Lys Lys Leu
465	470	475
Phe Gly Thr Ser Gly Gln	Lys Thr Lys Ile Ser	Asn Arg Gly Glu
	485	490
Asn Ser Cys Lys Ala Thr	Gly Gln Val Cys His	Ala Leu Cys Ser Pro



			500						505						510		
Glu	Gly	Cys	Trp	Gly	Pro	Glu	Pro	Arg	Asp	Cys	Val	Ser	Cys	Arg	Asn		
		515					520					525					
Val	Ser	Arg	Gly	Arg	Glu	Cys	Val	Asp	Lys	Cys	Asn	Leu	Leu	Glu	Gly		
		530					535				540						
Glu	Pro	Arg	Glu	Phe	Val	Glu	Asn	Ser	Glu	Cys	Ile	Gln	Cys	His	Pro		
545					550					555					560		
Glu	Cys	Leu	Pro	Gln	Ala	Met	Asn	Ile	Thr	Cys	Thr	Gly	Arg	Gly	Pro		
				565					570					575			
Asp	Asn	Cys	Ile	Gln	Cys	Ala	His	Tyr	Ile	Asp	Gly	Pro	His	Cys	Val		
			580					585				590					
Lys	Thr	Cys	Pro	Ala	Gly	Val	Met	Gly	Glu	Asn	Asn	Thr	Leu	Val	Trp		
		595					600					605					
Lys	Tyr	Ala	Asp	Ala	Gly	His	Val	Cys	His	Leu	Cys	His	Pro	Asn	Cys		
		610					615				620						
Thr	Tyr	Gly	Cys	Thr	Gly	Pro	Gly	Leu	Glu	Gly	Cys	Pro	Thr	Asn	Gly		
625					630					635					640		
Pro	Lys	Ile	Pro	Ser	Ile	Ala	Thr	Gly	Met	Val	Gly	Ala	Leu	Leu	Leu		
				645					650					655			
Leu	Leu	Val	Val	Ala	Leu	Gly	Ile	Gly	Leu	Phe	Met	Arg	Arg	Arg	His		
			660					665				670					
Ile	Val	Arg	Lys	Arg	Thr	Leu	Arg	Arg	Leu	Leu	Gln	Glu	Arg	Glu	Leu		
		675					680					685					
Val	Glu	Pro	Leu	Thr	Pro	Ser	Gly	Glu	Ala	Pro	Asn	Gln	Ala	Leu	Leu		
		690					695				700						
Arg	Ile	Leu	Lys	Glu	Thr	Glu	Phe	Lys	Lys	Ile	Lys	Val	Leu	Gly	Ser		
705					710					715					720		
Gly	Ala	Phe	Gly	Thr	Val	Tyr	Lys	Gly	Leu	Trp	Ile	Pro	Glu	Gly	Glu		
				725					730					735			
Lys	Val	Lys	Ile	Pro	Val	Ala	Ile	Lys	Glu	Leu	Arg	Glu	Ala	Thr	Ser		
			740					745				750					
Pro	Lys	Ala	Asn	Lys	Glu	Ile	Leu	Asp	Glu	Ala	Tyr	Val	Met	Ala	Ser		
		755					760					765					
Val	Asp	Asn	Pro	His	Val	Cys	Arg	Leu	Leu	Gly	Ile	Cys	Leu	Thr	Ser		
		770					775				780						
Thr	Val	Gln	Leu	Ile	Thr	Gln	Leu	Met	Pro	Phe	Gly	Cys	Leu	Leu	Asp		
785					790					795					800		
Tyr	Val	Arg	Glu	His	Lys	Asp	Asn	Ile	Gly	Ser	Gln	Tyr	Leu	Leu	Asn		
				805					810					815			
Trp	Cys	Val	Gln	Ile	Ala	Lys	Gly	Met	Asn	Tyr	Leu	Glu	Asp	Arg	Arg		
			820					825				830					
Leu	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Val	Leu	Val	Lys	Thr	Pro		
		835					840					845					
Gln	His	Val	Lys	Ile	Thr	Asp	Phe	Gly	Leu	Ala	Lys	Leu	Leu	Gly	Ala		
		850					855										

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945          950          955          960
Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met Ala Arg Asp Pro Gln
          965          970          975
Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro Ser Pro
          980          985          990
Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp Met Asp
          995          1000          1005
Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln Gly Phe Phe
          1010          1015          1020
Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu Ser Ser Leu Ser Ala
          1025          1030          1035          1040
Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp Arg Asn Gly Leu Gln
          1045          1050          1055
Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln Arg Tyr Ser Ser Asp
          1060          1065          1070
Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp Asp Thr Phe Leu Pro
          1075          1080          1085
Val Pro Glu Tyr Ile Asn Gln Ser Val Pro Lys Arg Pro Ala Gly Ser
          1090          1095          1100
Val Gln Asn Pro Val Tyr His Asn Gln Pro Leu Asn Pro Ala Pro Ser
          1105          1110          1115          1120
Arg Asp Pro His Tyr Gln Asp Pro His Ser Thr Ala Val Gly Asn Pro
          1125          1130          1135
Glu Tyr Leu Asn Thr Val Gln Pro Thr Cys Val Asn Ser Thr Phe Asp
          1140          1145          1150
Ser Pro Ala His Trp Ala Gln Lys Gly Ser His Gln Ile Ser Leu Asp
          1155          1160          1165
Asn Pro Asp Tyr Gln Gln Asp Phe Phe Pro Lys Glu Ala Lys Pro Asn
          1170          1175          1180
Gly Ile Phe Lys Gly Ser Thr Ala Glu Asn Ala Glu Tyr Leu Arg Val
          1185          1190          1195          1200
Ala Pro Gln Ser Ser Glu Phe Ile Gly Ala
          1205          1210

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<210> 253  
 <211> 976  
 <212> PRT  
 <213> Homo sapiens

<300>  
 <308> GenBank No. NP005223  
 <309> 2004-11-29

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Met Glu Arg Arg Trp Pro Leu Gly Leu Gly Leu Val Leu Leu Leu Cys
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Ala Pro Leu Pro Pro Gly Ala Arg Ala Lys Glu Val Thr Leu Met Asp
          20          25          30
Thr Ser Lys Ala Gln Gly Glu Leu Gly Trp Leu Leu Asp Pro Pro Lys
          35          40          45
Asp Gly Trp Ser Glu Gln Gln Gln Ile Leu Asn Gly Thr Pro Leu Tyr
          50          55          60
Met Tyr Gln Asp Cys Pro Met Gln Gly Arg Arg Asp Thr Asp His Trp
          65          70          75          80
Leu Arg Ser Asn Trp Ile Tyr Arg Gly Glu Glu Ala Ser Arg Val His

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					85					90					95	
Val	Glu	Leu	Gln	Phe	Thr	Val	Arg	Asp	Cys	Lys	Ser	Phe	Pro	Gly	Gly	
			100					105					110			
Ala	Gly	Pro	Leu	Gly	Cys	Lys	Glu	Thr	Phe	Asn	Leu	Leu	Tyr	Met	Glu	
			115					120					125			
Ser	Asp	Gln	Asp	Val	Gly	Ile	Gln	Leu	Arg	Arg	Pro	Leu	Phe	Gln	Lys	
			130					135					140			
Val	Thr	Thr	Val	Ala	Ala	Asp	Gln	Ser	Phe	Thr	Ile	Arg	Asp	Leu	Ala	
145						150					155				160	
Ser	Gly	Ser	Val	Lys	Leu	Asn	Val	Glu	Arg	Cys	Ser	Leu	Gly	Arg	Leu	
				165					170					175		
Thr	Arg	Arg	Gly	Leu	Tyr	Leu	Ala	Phe	His	Asn	Pro	Gly	Ala	Cys	Val	
			180					185					190			
Ala	Leu	Val	Ser	Val	Arg	Val	Phe	Tyr	Gln	Arg	Cys	Pro	Glu	Thr	Leu	
			195					200					205			
Asn	Gly	Leu	Ala	Gln	Phe	Pro	Asp	Thr	Leu	Pro	Gly	Pro	Ala	Gly	Leu	
			210				215					220				
Val	Glu	Val	Ala	Gly	Thr	Cys	Leu	Pro	His	Ala	Arg	Ala	Ser	Pro	Arg	
225						230					235				240	
Pro	Ser	Gly	Ala	Pro	Arg	Met	His	Cys	Ser	Pro	Asp	Gly	Glu	Trp	Leu	
				245					250					255		
Val	Pro	Val	Gly	Arg	Cys	His	Cys	Glu	Pro	Gly	Tyr	Glu	Glu	Gly	Gly	
			260					265					270			
Ser	Gly	Glu	Ala	Cys	Val	Ala	Cys	Pro	Ser	Gly	Ser	Tyr	Arg	Met	Asp	
			275				280					285				
Met	Asp	Thr	Pro	His	Cys	Leu	Thr	Cys	Pro	Gln	Gln	Ser	Thr	Ala	Glu	
			290				295					300				
Ser	Glu	Gly	Ala	Thr	Ile	Cys	Thr	Cys	Glu	Ser	Gly	His	Tyr	Arg	Ala	
305					310						315				320	
Pro	Gly	Glu	Gly	Pro	Gln	Val	Ala	Cys	Thr	Gly	Pro	Pro	Ser	Ala	Pro	
				325							330			335		
Arg	Asn	Leu	Ser	Phe	Ser	Ala	Ser	Gly	Thr	Gln	Leu	Ser	Leu	Arg	Trp	
			340					345					350			
Glu	Pro	Pro	Ala	Asp	Thr	Gly	Gly	Arg	Gln	Asp	Val	Arg	Tyr	Ser	Val	
			355				360					365				
Arg	Cys	Ser	Gln	Cys	Gln	Gly	Thr	Ala	Gln	Asp	Gly	Gly	Pro	Cys	Gln	
			370				375					380				
Pro	Cys	Gly	Val	Gly	Val	His	Phe	Ser	Pro	Gly	Ala	Arg	Gly	Leu	Thr	
385					390					395					400	
Thr	Pro	Ala	Val	His	Val	Asn	Gly	Leu	Glu	Pro	Tyr	Ala	Asn	Tyr	Thr	
				405						410				415		
Phe	Asn	Val	Glu	Ala	Gln	Asn	Gly	Val	Ser	Gly	Leu	Gly	Ser	Ser	Gly	
			420					425								

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530	535	540
Gly Gly Glu Ile Val Ala Val Ile Phe Gly Leu Leu Leu Gly Ala Ala		
545	550	555
Leu Leu Leu Gly Ile Leu Val Phe Arg Ser Arg Arg Ala Gln Arg Gln		
	565	570
Arg Gln Gln Arg Gln Arg Asp Arg Ala Thr Asp Val Asp Arg Glu Asp		575
	580	585
Lys Leu Trp Leu Lys Pro Tyr Val Asp Leu Gln Ala Tyr Glu Asp Pro		590
	595	600
Ala Gln Gly Ala Leu Asp Phe Thr Arg Glu Leu Asp Pro Ala Trp Leu		605
	610	615
Met Val Asp Thr Val Ile Gly Glu Gly Glu Phe Gly Glu Val Tyr Arg		620
625	630	635
Gly Thr Leu Arg Leu Pro Ser Gln Asp Cys Lys Thr Val Ala Ile Lys		640
	645	650
Thr Leu Lys Asp Thr Ser Pro Gly Gly Gln Trp Trp Asn Phe Leu Arg		655
	660	665
Glu Ala Thr Ile Met Gly Gln Phe Ser His Pro His Ile Leu His Leu		670
	675	680
Glu Gly Val Val Thr Lys Arg Lys Pro Ile Met Ile Ile Thr Glu Phe		685
	690	695
Met Glu Asn Gly Ala Leu Asp Ala Phe Leu Arg Glu Arg Glu Asp Gln		700
705	710	715
Leu Val Pro Gly Gln Leu Val Ala Met Leu Gln Gly Ile Ala Ser Gly		720
	725	730
Met Asn Tyr Leu Ser Asn His Asn Tyr Val His Arg Asp Leu Ala Ala		735
	740	745
Arg Asn Ile Leu Val Asn Gln Asn Leu Cys Cys Lys Val Ser Asp Phe		750
	755	760
Gly Leu Thr Arg Leu Leu Asp Phe Asp Gly Thr Tyr Glu Thr Gln		765
	770	775
Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Ala His		780
785	790	795
Arg Ile Phe Thr Thr Ala Ser Asp Val Trp Ser Phe Gly Ile Val Met		800
	805	810
Trp Glu Val Leu Ser Phe Gly Asp Lys Pro Tyr Gly Glu Met Ser Asn		815
	820	825
Gln Glu Val Met Lys Ser Ile Glu Asp Gly Tyr Arg Leu Pro Pro Pro		830
	835	840
Val Asp Cys Pro Ala Pro Leu Tyr Glu Leu Met Lys Asn Cys Trp Ala		845
	850	855
Tyr Asp Arg Ala Arg Arg Pro His Phe Gln Lys Leu Gln Ala His Leu		860
865	870	875
Glu Gln Leu Leu Ala Asn Pro His Ser Leu Arg Thr Ile Ala Asn Phe		880
	885	890
Asp Pro Arg Met Thr Leu Arg Leu Pro Ser Leu Ser Gly Ser Asp Gly		895
	900	905
Ile Pro Tyr Arg Thr Val Ser Glu Trp Leu Glu Ser Ile Arg Met Lys		910
	915	920
Arg Tyr Ile Leu His Phe His Ser Ala Gly Leu Asp Thr Met Glu Cys		925
	930	935
Val Leu Glu Leu Thr Ala Glu Asp Leu Thr Gln Met Gly Ile Thr Leu		940
945	950	955
Pro Gly His Gln Lys Arg Ile Leu Cys Ser Ile Gln Gly Phe Lys Asp		960
	965	970
		975

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<210> 254  
 <211> 976  
 <212> PRT  
 <213> Homo sapiens

<300>  
 <308> GenBank No. NP004422  
 <309> 2004-12-20

<400> 254  
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 Ala Leu Ala Ala Ala Ala Ala Ala Gln Gly Lys Glu Val Val Leu Leu  
 20 25 30  
 Asp Phe Ala Ala Ala Gly Gly Glu Leu Gly Trp Leu Thr His Pro Tyr  
 35 40 45  
 Gly Lys Gly Trp Asp Leu Met Gln Asn Ile Met Asn Asp Met Pro Ile  
 50 55 60  
 Tyr Met Tyr Ser Val Cys Asn Val Met Ser Gly Asp Gln Asp Asn Trp  
 65 70 75 80  
 Leu Arg Thr Asn Trp Val Tyr Arg Gly Glu Ala Glu Arg Ile Phe Ile  
 85 90 95  
 Glu Leu Lys Phe Thr Val Arg Asp Cys Asn Ser Phe Pro Gly Gly Ala  
 100 105 110  
 Ser Ser Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Ala Glu Ser Asp Leu  
 115 120 125  
 Asp Tyr Gly Thr Asn Phe Gln Lys Arg Leu Phe Thr Lys Ile Asp Thr  
 130 135 140  
 Ile Ala Pro Asp Glu Ile Thr Val Ser Ser Asp Phe Glu Ala Arg His  
 145 150 155 160  
 Val Lys Leu Asn Val Glu Glu Arg Ser Val Gly Pro Leu Thr Arg Lys  
 165 170 175  
 Gly Phe Tyr Leu Ala Phe Gln Asp Ile Gly Ala Cys Val Ala Leu Leu  
 180 185 190  
 Ser Val Arg Val Tyr Tyr Lys Lys Cys Pro Glu Leu Leu Gln Gly Leu  
 195 200 205  
 Ala His Phe Pro Glu Thr Ile Ala Gly Ser Asp Ala Pro Ser Leu Ala  
 210 215 220  
 Thr Val Ala Gly Thr Cys Val Asp His Ala Val Val Pro Pro Gly Gly  
 225 230 235 240  
 Glu Glu Pro Arg Met His Cys Ala Val Asp Gly Glu Trp Leu Val Pro  
 245 250 255  
 Ile Gly Gln Cys Leu Cys Gln Ala Gly Tyr Glu Lys Val Glu Asp Ala  
 260 265 270  
 Cys Gln Ala Cys Ser Pro Gly Phe Phe Lys Phe Glu Ala Ser Glu Ser  
 275 280 285  
 Pro Cys Leu Glu Cys Pro Glu His Thr Leu Pro Ser Pro Glu Gly Ala  
 290 295 300  
 Thr Ser Cys Glu Cys Glu Glu Gly Phe Phe Arg Ala Pro Gln Asp Pro  
 305 310 315 320  
 Ala Ser Met Pro Cys Thr Arg Pro Pro Ser Ala Pro His Tyr Leu Thr  
 325 330 335  
 Ala Val Gly Met Gly Ala Lys Val Glu Leu Arg Trp Thr Pro Pro Gln  
 340 345 350  
 Asp Ser Gly Gly Arg Glu Asp Ile Val Tyr Ser Val Thr Cys Glu Gln

			355							360							365			
Cys	Trp	Pro	Glu	Ser	Gly	Glu	Cys	Gly	Pro	Cys	Glu	Ala	Ser	Val	Arg					
	370					375				380										
Tyr	Ser	Glu	Pro	Pro	His	Gly	Leu	Thr	Arg	Thr	Ser	Val	Thr	Val	Ser					
385					390					395					400					
Asp	Leu	Glu	Pro	His	Met	Asn	Tyr	Thr	Phe	Thr	Val	Glu	Ala	Arg	Asn					
				405					410					415						
Gly	Val	Ser	Gly	Leu	Val	Thr	Ser	Arg	Ser	Phe	Arg	Thr	Ala	Ser	Val					
			420					425					430							
Ser	Ile	Asn	Gln	Thr	Glu	Pro	Pro	Lys	Val	Arg	Leu	Glu	Gly	Arg	Ser					
		435				440					445									
Thr	Thr	Ser	Leu	Ser	Val	Ser	Trp	Ser	Ile	Pro	Pro	Pro	Gln	Gln	Ser					
	450					455				460										
Arg	Val	Trp	Lys	Tyr	Glu	Val	Thr	Tyr	Arg	Lys	Lys	Gly	Asp	Ser	Asn					
465					470				475						480					
Ser	Tyr	Asn	Val	Arg	Arg	Thr	Glu	Gly	Phe	Ser	Val	Thr	Leu	Asp	Asp					
				485					490				495							
Leu	Ala	Pro	Asp	Thr	Thr	Tyr	Leu	Val	Gln	Val	Gln	Ala	Leu	Thr	Gln					
			500					505					510							
Glu	Gly	Gln	Gly	Ala	Gly	Ser	Lys	Val	His	Glu	Phe	Gln	Thr	Leu	Ser					
		515				520				525										
Pro	Glu	Gly	Ser	Gly	Asn	Leu	Ala	Val	Ile	Gly	Gly	Val	Ala	Val	Gly					
	530					535				540										
Val	Val	Leu	Leu	Leu	Val	Leu	Ala	Gly	Val	Gly	Phe	Phe	Ile	His	Arg					
545					550					555					560					
Arg	Arg	Lys	Asn	Gln	Arg	Ala	Arg	Gln	Ser	Pro	Glu	Asp	Val	Tyr	Phe					
				565					570					575						
Ser	Lys	Ser	Glu	Gln	Leu	Lys	Pro	Leu	Lys	Thr	Tyr	Val	Asp	Pro	His					
			580					585					590							
Thr	Tyr	Glu	Asp	Pro	Asn	Gln	Ala	Val	Leu	Lys	Phe	Thr	Thr	Glu	Ile					
		595				600						605								
His	Pro	Ser	Cys	Val	Thr	Arg	Gln	Lys	Val	Ile	Gly	Ala	Gly	Glu	Phe					
	610					615					620									
Gly	Glu	Val	Tyr	Lys	Gly	Met	Leu	Lys	Thr	Ser	Ser	Gly	Lys	Lys	Glu					
625					630					635					640					
Val	Pro	Val	Ala	Ile	Lys	Thr	Leu	Lys	Ala	Gly	Tyr	Thr	Glu	Lys	Gln					
				645					650				655							
Arg	Val	Asp	Phe	Leu	Gly	Glu	Ala	Gly	Ile	Met	Gly	Gln	Phe	Ser	His					
			660					665					670							
His	Asn	Ile	Ile	Arg	Leu	Glu	Gly	Val	Ile	Ser	Lys									

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				805					810					815	
Pro	Tyr	Trp	Glu	Leu	Ser	Asn	His	Glu	Val	Met	Lys	Ala	Ile	Asn	Asp
			820						825					830	
Gly	Phe	Arg	Leu	Pro	Thr	Pro	Met	Asp	Cys	Pro	Ser	Ala	Ile	Tyr	Gln
		835					840					845			
Leu	Met	Met	Gln	Cys	Trp	Gln	Gln	Glu	Arg	Ala	Arg	Arg	Pro	Lys	Phe
	850					855					860				
Ala	Asp	Ile	Val	Ser	Ile	Leu	Asp	Lys	Leu	Ile	Arg	Ala	Pro	Asp	Ser
865					870					875				880	
Leu	Lys	Thr	Leu	Ala	Asp	Phe	Asp	Pro	Arg	Val	Ser	Ile	Arg	Leu	Pro
			885						890					895	
Ser	Thr	Ser	Gly	Ser	Glu	Gly	Val	Pro	Phe	Arg	Thr	Val	Ser	Glu	Trp
		900						905					910		
Leu	Glu	Ser	Ile	Lys	Met	Gln	Gln	Tyr	Thr	Glu	His	Phe	Met	Ala	Ala
	915						920					925			
Gly	Tyr	Thr	Ala	Ile	Glu	Lys	Val	Val	Gln	Met	Thr	Asn	Asp	Asp	Ile
	930					935						940			
Lys	Arg	Ile	Gly	Val	Arg	Leu	Pro	Gly	His	Gln	Lys	Arg	Ile	Ala	Tyr
945					950					955				960	
Ser	Leu	Leu	Gly	Leu	Lys	Asp	Gln	Val	Asn	Thr	Val	Gly	Ile	Pro	Ile
				965					970					975	

&lt;210&gt; 255

&lt;211&gt; 983

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. NP005224

&lt;309&gt; 2004-11-16

&lt;400&gt; 255

Met	Asp	Cys	Gln	Leu	Ser	Ile	Leu	Leu	Leu	Leu	Ser	Cys	Ser	Val	Leu
1				5					10					15	
Asp	Ser	Phe	Gly	Glu	Leu	Ile	Pro	Gln	Pro	Ser	Asn	Glu	Val	Asn	Leu
		20						25					30		
Leu	Asp	Ser	Lys	Thr	Ile	Gln	Gly	Glu	Leu	Gly	Trp	Ile	Ser	Tyr	Pro
	35					40					45				
Ser	His	Gly	Trp	Glu	Glu	Ile	Ser	Gly	Val	Asp	Glu	His	Tyr	Thr	Pro
50						55					60				
Ile	Arg	Thr	Tyr	Gln	Val	Cys	Asn	Val	Met	Asp	His	Ser	Gln	Asn	Asn
65				70						75				80	
Trp	Leu	Arg	Thr	Asn	Trp	Val	Pro	Arg	Asn	Ser	Ala	Gln	Lys	Ile	Tyr
			85						90					95	
Val	Glu	Leu	Lys	Phe	Thr	Leu	Arg	Asp	Cys	Asn	Ser	Ile	Pro	Leu	Val
		100						105					110		
Leu	Gly	Thr	Cys	Lys	Glu	Thr	Phe	Asn	Leu	Tyr	Tyr	Met	Glu	Ser	Asp
	115						120					125			
Asp	Asp	His	Gly	Val	Lys	Phe	Arg	Glu	His	Gln	Phe	Thr	Lys	Ile	Asp
	130					135					140				
Thr	Ile	Ala	Ala	Asp	Glu	Ser	Phe	Thr	Gln	Met	Asp	Leu	Gly	Asp	Arg
145				150						155				160	
Ile	Leu	Lys	Leu	Asn	Thr	Glu	Ile	Arg	Glu	Val	Gly	Pro	Val	Asn	Lys
			165						170					175	
Lys	Gly	Phe	Tyr	Leu	Ala	Phe	Gln	Asp	Val	Gly	Ala	Cys	Val	Ala	Leu

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			180					185					190				
Val	Ser	Val	Arg	Val	Tyr	Phe	Lys	Lys	Cys	Pro	Phe	Thr	Val	Lys	Asn		
		195					200						205				
Leu	Ala	Met	Phe	Pro	Asp	Thr	Val	Pro	Met	Asp	Ser	Gln	Ser	Leu	Val		
		210					215					220					
Glu	Val	Arg	Gly	Ser	Cys	Val	Asn	Asn	Ser	Lys	Glu	Glu	Asp	Pro	Pro		
225					230					235					240		
Arg	Met	Tyr	Cys	Ser	Thr	Glu	Gly	Glu	Trp	Leu	Val	Pro	Ile	Gly	Lys		
				245					250					255			
Cys	Ser	Cys	Asn	Ala	Gly	Tyr	Glu	Glu	Arg	Gly	Phe	Met	Cys	Gln	Ala		
			260					265					270				
Cys	Arg	Pro	Gly	Phe	Tyr	Lys	Ala	Leu	Asp	Gly	Asn	Met	Lys	Cys	Ala		
		275					280					285					
Lys	Cys	Pro	Pro	His	Ser	Ser	Thr	Gln	Glu	Asp	Gly	Ser	Met	Asn	Cys		
		290				295					300						
Arg	Cys	Glu	Asn	Asn	Tyr	Phe	Arg	Ala	Asp	Lys	Asp	Pro	Pro	Ser	Met		
305					310					315					320		
Ala	Cys	Thr	Arg	Pro	Pro	Ser	Ser	Pro	Arg	Asn	Val	Ile	Ser	Asn	Ile		
				325					330					335			
Asn	Glu	Thr	Ser	Val	Ile	Leu	Asp	Trp	Ser	Trp	Pro	Leu	Asp	Thr	Gly		
		340						345					350				
Gly	Arg	Lys	Asp	Val	Thr	Phe	Asn	Ile	Ile	Cys	Lys	Lys	Cys	Gly	Trp		
		355					360					365					
Asn	Ile	Lys	Gln	Cys	Glu	Pro	Cys	Ser	Pro	Asn	Val	Arg	Phe	Leu	Pro		
		370				375				380							
Arg	Gln	Phe	Gly	Leu	Thr	Asn	Thr	Thr	Val	Thr	Val	Thr	Asp	Leu	Leu		
385				390					395						400		
Ala	His	Thr	Asn	Tyr	Thr	Phe	Glu	Ile	Asp	Ala	Val	Asn	Gly	Val	Ser		
				405					410					415			
Glu	Leu	Ser	Ser	Pro	Pro	Arg	Gln	Phe	Ala	Ala	Val	Ser	Ile	Thr	Thr		
			420					425					430				
Asn	Gln	Ala	Ala	Pro	Ser	Pro	Val	Leu	Thr	Ile	Lys	Lys	Asp	Arg	Thr		
		435					440					445					
Ser	Arg	Asn	Ser	Ile	Ser	Leu	Ser	Trp	Gln	Glu	Pro	Glu	His	Pro	Asn		
		450				455				460							
Gly	Ile	Ile	Leu	Asp	Tyr	Glu	Val	Lys	Tyr	Tyr	Glu	Lys	Gln	Glu	Gln		
465				470					475						480		
Glu	Thr	Ser	Tyr	Thr	Ile	Leu	Arg	Ala	Arg	Gly	Thr	Asn	Val	Thr	Ile		
				485					490					495			
Ser	Ser	Leu	Lys	Pro	Asp	Thr	Ile	Tyr	Val	Phe	Gln	Ile	Arg	Ala	Arg		
			500					505					510				
Thr	Ala	Ala	Gly	Tyr	Gly	Thr	Asn	Ser	Arg	Lys	Phe	Glu	Phe	Glu	Thr		
		515					520					525					
Ser	Pro	Asp	Ser	Phe	Ser	Ile	Ser	Gly	Glu	Ser	Ser	Gln	Val	Val	Met		
		530				535				540							
Ile	Ala	Ile	Ser	Ala	Ala	Val	Ala	Ile	Ile	Leu	Leu	Thr	Val	Val	Ile		
545				550					555						560		
Tyr	Val	Leu	Ile	Gly	Arg	Phe	Cys	Gly	Tyr	Lys	Ser	Lys	His	Gly	Ala		
				565				570						575			
Asp	Glu	Lys	Arg	Leu	His	Phe	Gly	Asn	Gly	His	Leu	Lys	Leu	Pro	Gly		
			580				585					590					
Leu	Arg	Thr	Tyr	Val	Asp	Pro	His	Thr	Tyr	Glu	Asp	Pro	Thr	Gln	Ala		
		595				600						605					
Val	His	Glu	Phe	Ala	Lys	Glu	Leu	Asp	Ala	Thr	Asn	Ile	Ser	Ile	Asp		
		610				615					620						
Lys	Val	Val	Gly	Ala	Gly	Glu	Phe	Gly	Glu	Val	Cys	Ser	Gly	Arg	Leu		



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625					630					635				640
Lys	Leu	Pro	Ser	Lys	Lys	Glu	Ile	Ser	Val	Ala	Ile	Lys	Thr	Lys
				645					650					655
Val	Gly	Tyr	Thr	Glu	Lys	Gln	Arg	Arg	Asp	Phe	Leu	Gly	Glu	Ala
				660				665					670	
Ile	Met	Gly	Gln	Phe	Asp	His	Pro	Asn	Ile	Ile	Arg	Leu	Glu	Gly
		675				680					685			Val
Val	Thr	Lys	Ser	Lys	Pro	Val	Met	Ile	Val	Thr	Glu	Tyr	Met	Glu
	690					695					700			Asn
Gly	Ser	Leu	Asp	Ser	Phe	Leu	Arg	Lys	His	Asp	Ala	Gln	Phe	Thr
705					710					715				720
Ile	Gln	Leu	Val	Gly	Met	Leu	Arg	Gly	Ile	Ala	Ser	Gly	Met	Lys
				725				730					735	Tyr
Leu	Ser	Asp	Met	Gly	Tyr	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn
			740					745					750	Ile
Leu	Ile	Asn	Ser	Asn	Leu	Val	Cys	Lys	Val	Ser	Asp	Phe	Gly	Leu
	755						760					765		Ser
Arg	Val	Leu	Glu	Asp	Asp	Pro	Glu	Ala	Ala	Tyr	Thr	Thr	Arg	Gly
	770					775					780			Gly
Lys	Ile	Pro	Ile	Arg	Trp	Thr	Ser	Pro	Glu	Ala	Ile	Ala	Tyr	Arg
785					790					795				Lys
Phe	Thr	Ser	Ala	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Ile	Val	Leu	Trp
				805					810					Glu
Val	Met	Ser	Tyr	Gly	Glu	Arg	Pro	Tyr	Trp	Glu	Met	Ser	Asn	Gln
			820					825					830	Asp
Val	Ile	Lys	Ala	Val	Asp	Glu	Gly	Tyr	Arg	Leu	Pro	Pro	Pro	Met
	835						840					845		Asp
Cys	Pro	Ala	Ala	Leu	Tyr	Gln	Leu	Met	Leu	Asp	Cys	Trp	Gln	Lys
	850					855				860				Asp
Arg	Asn	Asn	Arg	Pro	Lys	Phe	Glu	Gln	Ile	Val	Ser	Ile	Leu	Asp
865					870					875				Lys
Leu	Ile	Arg	Asn	Pro	Gly	Ser	Leu	Lys	Ile	Ile	Thr	Ser	Ala	Ala
			885						890					Ala
Arg	Pro	Ser	Asn	Leu	Leu	Leu	Asp	Gln	Ser	Asn	Val	Asp	Ile	Thr
			900					905					910	Thr
Phe	Arg	Thr	Thr	Gly	Asp	Trp	Leu	Asn	Gly	Val	Trp	Thr	Ala	His
		915					920					925		Cys
Lys	Glu	Ile	Phe	Thr	Gly	Val	Glu	Tyr	Ser	Ser	Cys	Asp	Thr	Ile
	930					935					940			Ala
Lys	Ile	Ser	Thr	Asp	Asp	Met	Lys	Lys	Val	Gly	Val	Thr	Val	Val
945					950					955				Gly
Pro	Gln	Lys	Lys	Ile	Ile	Ser	Ser	Ile	Lys	Ala	Leu	Glu	Thr	Gln
				965					970					Ser
Lys	Asn	Gly	Pro	Val	Pro	Val								
				980										

&lt;210&gt; 256

&lt;211&gt; 986

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. NP004429

&lt;309&gt; 2004-11-16

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&lt;400&gt; 256

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Met Ala Gly Ile Phe Tyr Phe Ala Leu Phe Ser Cys Leu Phe Gly Ile
 1      5      10      15
Cys Asp Ala Val Thr Gly Ser Arg Val Tyr Pro Ala Asn Glu Val Thr
      20      25      30
Leu Leu Asp Ser Arg Ser Val Gln Gly Glu Leu Gly Trp Ile Ala Ser
      35      40      45
Pro Leu Glu Gly Gly Trp Glu Glu Val Ser Ile Met Asp Glu Lys Asn
      50      55      60
Thr Pro Ile Arg Thr Tyr Gln Val Cys Asn Val Met Glu Pro Ser Gln
      65      70      75      80
Asn Asn Trp Leu Arg Thr Asp Trp Ile Thr Arg Glu Gly Ala Gln Arg
      85      90      95
Val Tyr Ile Glu Ile Lys Phe Thr Leu Arg Asp Cys Asn Ser Leu Pro
      100      105      110
Gly Val Met Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Tyr Glu
      115      120      125
Ser Asp Asn Asp Lys Glu Arg Phe Ile Arg Glu Asn Gln Phe Val Lys
      130      135      140
Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Val Asp Ile Gly
      145      150      155      160
Asp Arg Ile Met Lys Leu Asn Thr Glu Ile Arg Asp Val Gly Pro Leu
      165      170      175
Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys Ile
      180      185      190
Ala Leu Val Ser Val Arg Val Phe Tyr Lys Lys Cys Pro Leu Thr Val
      195      200      205
Arg Asn Leu Ala Gln Phe Pro Asp Thr Ile Thr Gly Ala Asp Thr Ser
      210      215      220
Ser Leu Val Glu Val Arg Gly Ser Cys Val Asn Asn Ser Glu Glu Lys
      225      230      235      240
Asp Val Pro Lys Met Tyr Cys Gly Ala Asp Gly Glu Trp Leu Val Pro
      245      250      255
Ile Gly Asn Cys Leu Cys Asn Ala Gly His Glu Glu Arg Ser Gly Glu
      260      265      270
Cys Gln Ala Cys Lys Ile Gly Tyr Tyr Lys Ala Leu Ser Thr Asp Ala
      275      280      285
Thr Cys Ala Lys Cys Pro Pro His Ser Tyr Ser Val Trp Glu Gly Ala
      290      295      300
Thr Ser Cys Thr Cys Asp Arg Gly Phe Phe Arg Ala Asp Asn Asp Ala
      305      310      315      320
Ala Ser Met Pro Cys Thr Arg Pro Pro Ser Ala Pro Leu Asn Leu Ile
      325      330      335
Ser Asn Val Asn Glu Thr Ser Val Asn Leu Glu Trp Ser Ser Pro Gln
      340      345      350
Asn Thr Gly Gly Arg Gln Asp Ile Ser Tyr Asn Val Val Cys Lys Lys
      355      360      365
Cys Gly Ala Gly Asp Pro Ser Lys Cys Arg Pro Cys Gly Ser Gly Val
      370      375      380
His Tyr Thr Pro Gln Gln Asn Gly Leu Lys Thr Thr Lys Val Ser Ile
      385      390      395      400
Thr Asp Leu Leu Ala His Thr Asn Tyr Thr Phe Glu Ile Trp Ala Val
      405      410      415
Asn Gly Val Ser Lys Tyr Asn Pro Asn Pro Asp Gln Ser Val Ser Val
      420      425      430
Thr Val Thr Thr Asn Gln Ala Ala Pro Ser Ser Ile Ala Leu Val Gln

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		435					440					445						
Ala	Lys	Glu	Val	Thr	Arg	Tyr	Ser	Val	Ala	Leu	Ala	Trp	Leu	Glu	Pro			
	450					455					460							
Asp	Arg	Pro	Asn	Gly	Val	Ile	Leu	Glu	Tyr	Glu	Val	Lys	Tyr	Tyr	Glu			
465					470					475					480			
Lys	Asp	Gln	Asn	Glu	Arg	Ser	Tyr	Arg	Ile	Val	Arg	Thr	Ala	Ala	Arg			
				485					490					495				
Asn	Thr	Asp	Ile	Lys	Gly	Leu	Asn	Pro	Leu	Thr	Ser	Tyr	Val	Phe	His			
			500					505					510					
Val	Arg	Ala	Arg	Thr	Ala	Ala	Gly	Tyr	Gly	Asp	Phe	Ser	Glu	Pro	Leu			
		515					520					525						
Glu	Val	Thr	Thr	Asn	Thr	Val	Pro	Ser	Arg	Ile	Ile	Gly	Asp	Gly	Ala			
	530					535					540							
Asn	Ser	Thr	Val	Leu	Leu	Val	Ser	Val	Ser	Gly	Ser	Val	Val	Leu	Val			
545					550					555					560			
Val	Ile	Leu	Ile	Ala	Ala	Phe	Val	Ile	Ser	Arg	Arg	Arg	Ser	Lys	Tyr			
				565					570					575				
Ser	Lys	Ala	Lys	Gln	Glu	Ala	Asp	Glu	Glu	Lys	His	Leu	Asn	Gln	Gly			
			580					585					590					
Val	Arg	Thr	Tyr	Val	Asp	Pro	Phe	Thr	Tyr	Glu	Asp	Pro	Asn	Gln	Ala			
		595				600						605						
Val	Arg	Glu	Phe	Ala	Lys	Glu	Ile	Asp	Ala	Ser	Cys	Ile	Lys	Ile	Glu			
	610					615					620							
Lys	Val	Ile	Gly	Val	Gly	Glu	Phe	Gly	Glu	Val	Cys	Ser	Gly	Arg	Leu			
625					630				635					640				
Lys	Val	Pro	Gly	Lys	Arg	Glu	Ile	Cys	Val	Ala	Ile	Lys	Thr	Leu	Lys			
			645						650					655				
Ala	Gly	Tyr	Thr	Asp	Lys	Gln	Arg	Arg	Asp	Phe	Leu	Ser	Glu	Ala	Ser			
			660					665					670					
Ile	Met	Gly	Gln	Phe	Asp	His	Pro	Asn	Ile	Ile	His	Leu	Glu	Gly	Val			
		675				680						685						
Val	Thr	Lys	Cys	Lys	Pro	Val	Met	Ile	Ile	Thr	Glu	Tyr	Met	Glu	Asn			
	690					695					700							
Gly	Ser	Leu	Asp	Ala	Phe	Leu	Arg	Lys	Asn	Asp	Gly	Arg	Phe	Thr	Val			
705					710				715					720				
Ile	Gln	Leu	Val	Gly	Met	Leu	Arg	Gly	Ile	Gly	Ser	Gly	Met	Lys	Tyr			
			725						730					735				
Leu	Ser	Asp	Met	Ser	Tyr	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile			
		740						745					750					
Leu	Val	Asn	Ser	Asn	Leu	Val	Cys	Lys	Val	Ser	Asp	Phe	Gly	Met	Ser			
		755				760						765						
Arg	Val	Leu	Glu															

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				885					890					895					
Arg	Pro	Asn	Thr	Ala	Leu	Leu	Asp	Pro	Ser	Ser	Pro	Glu	Phe	Ser	Ala				
			900					905					910						
Val	Val	Ser	Val	Gly	Asp	Trp	Leu	Gln	Ala	Ile	Lys	Met	Asp	Arg	Tyr				
		915					920					925							
Lys	Asp	Asn	Phe	Thr	Ala	Ala	Gly	Tyr	Thr	Thr	Leu	Glu	Ala	Val	Val				
	930					935					940								
His	Val	Asn	Gln	Glu	Asp	Leu	Ala	Arg	Ile	Gly	Ile	Thr	Ala	Ile	Thr				
945					950					955					960				
His	Gln	Asn	Lys	Ile	Leu	Ser	Ser	Val	Gln	Ala	Met	Arg	Thr	Gln	Met				
			965						970					975					
Gln	Gln	Met	His	Gly	Arg	Met	Val	Pro	Val										
			980					985											

&lt;210&gt; 257

&lt;211&gt; 991

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. AAA74245

&lt;309&gt; 1995-08-10

&lt;400&gt; 257

Pro	Ala	Ser	Leu	Ala	Gly	Cys	Tyr	Ser	Ala	Pro	Arg	Arg	Ala	Pro	Leu				
1				5					10					15					
Trp	Thr	Cys	Leu	Leu	Leu	Cys	Ala	Ala	Leu	Arg	Thr	Leu	Leu	Ala	Ser				
		20					25					30							
Pro	Ser	Asn	Glu	Val	Asn	Leu	Leu	Asp	Ser	Arg	Thr	Val	Met	Gly	Asp				
		35				40					45								
Leu	Gly	Trp	Ile	Ala	Phe	Pro	Lys	Asn	Gly	Trp	Glu	Glu	Ile	Gly	Glu				
	50				55					60									
Val	Asp	Glu	Asn	Tyr	Ala	Pro	Ile	His	Thr	Tyr	Gln	Val	Cys	Lys	Val				
65				70					75					80					
Met	Glu	Gln	Asn	Gln	Asn	Asn	Trp	Leu	Leu	Thr	Ser	Trp	Ile	Ser	Asn				
			85					90					95						
Glu	Gly	Ala	Ser	Arg	Ile	Phe	Ile	Glu	Leu	Lys	Phe	Thr	Leu	Arg	Asp				
		100						105					110						
Cys	Asn	Ser	Leu	Pro	Gly	Gly	Leu	Gly	Thr	Cys	Lys	Glu	Thr	Phe	Asn				
		115					120					125							
Met	Tyr	Tyr	Phe	Glu	Ser	Asp	Asp	Gln	Asn	Gly	Arg	Asn	Ile	Lys	Glu				
	130					135				140									
Asn	Gln	Tyr	Ile	Lys	Ile	Asp	Thr	Ile	Ala	Ala	Asp	Glu	Ser	Phe	Thr				
145				150					155					160					
Glu	Leu	Asp	Leu	Gly	Asp	Arg	Val	Met	Lys	Leu	Asn	Thr	Glu	Val	Arg				
		165						170					175						
Asp	Val	Gly	Pro	Leu	Ser	Lys	Lys	Gly	Phe	Tyr	Leu	Ala	Phe	Gln	Asp				
		180						185					190						
Val	Gly	Ala	Cys	Ile	Ala	Leu	Val	Ser	Val	Arg	Val	Tyr	Tyr	Lys	Lys				
		195					200					205							
Cys	Pro	Ser	Val	Val	Arg	His	Leu	Ala	Val	Phe	Pro	Asp	Thr	Ile	Thr				
	210					215						220							
Gly	Ala	Asp	Ser	Ser	Gln	Leu	Leu	Glu	Val	Ser	Gly	Ser	Cys	Val	Asn				
225				230					235					240					
His	Ser	Val	Thr	Asp	Glu	Pro	Pro	Lys	Met	His	Cys	Ser	Ala	Glu	Gly				

Glu	Trp	Leu	Val	Pro	Ile	Gly	Lys	Cys	Met	Cys	Lys	Ala	Gly	Tyr	Glu
			260					265					270		
Glu	Lys	Asn	Gly	Thr	Cys	Gln	Val	Cys	Arg	Pro	Gly	Phe	Phe	Lys	Ala
			275					280					285		
Ser	Pro	His	Ile	Gln	Ser	Cys	Gly	Lys	Cys	Pro	Pro	His	Ser	Tyr	Thr
							295					300			
His	Glu	Glu	Ala	Ser	Thr	Ser	Cys	Val	Cys	Glu	Lys	Asp	Tyr	Phe	Arg
305							310					315			320
Arg	Glu	Ser	Asp	Pro	Thr	Met	Ala	Cys	Thr	Arg	Pro	Pro	Ser	Ala	
Pro	Arg	Asn	Ala	Ile	Ser	Asn	Val	Asn	Glu	Thr	Ser	Val	Phe	Leu	Glu
			340					345					350		
Trp	Ile	Pro	Pro	Ala	Asp	Thr	Gly	Arg	Lys	Asp	Val	Ser	Tyr	Tyr	
			355					360					365		
Ile	Ala	Cys	Lys	Lys	Cys	Asn	Ser	His	Ala	Gly	Val	Cys	Glu	Glu	Cys
			370					375					380		
Gly	Gly	His	Val	Arg	Tyr	Leu	Pro	Arg	Gln	Ser	Gly	Leu	Lys	Asn	Thr
385							390				395				400
Ser	Val	Met	Met	Val	Asp	Leu	Leu	Ala	His	Thr	Asn	Tyr	Thr	Phe	Glu
Ile	Glu	Ala	Val	Asn	Gly	Val	Ser	Asp	Leu	Ser	Pro	Gly	Ala	Arg	Gln
			420					425					430		
Tyr	Val	Ser	Val	Asn	Val	Thr	Thr	Asn	Gln	Ala	Ala	Pro	Ser	Pro	Val
			435					440					445		
Thr	Asn	Val	Lys	Lys	Gly	Lys	Ile	Ala	Lys	Asn	Ser	Ile	Ser	Leu	Ser
Trp	Gln	Glu	Pro	Asp	Arg	Pro	Asn	Gly	Ile	Ile	Leu	Glu	Tyr	Glu	Ile
465							470			475					480
Lys	His	Phe	Glu	Lys	Asp	Gln	Glu	Thr	Ser	Tyr	Thr	Ile	Ile	Lys	Ser
Lys	Glu	Thr	Thr	Ile	Thr	Ala	Glu	Gly	Leu	Lys	Pro	Ala	Ser	Val	Tyr
Val	Phe	Gln	Ile	Arg	Ala	Arg	Thr	Ala	Ala	Gly	Tyr	Gly	Val	Phe	Ser
Arg	Arg	Phe	Glu	Phe	Glu	Thr	Thr	Pro	Val	Phe	Ala	Ala	Ser	Ser	Asp
Gln	Ser	Gln	Ile	Pro	Val	Ile	Ala	Val	Ser	Val	Thr	Val	Gly	Val	Ile
545							550			555					560
Leu	Leu	Ala	Val	Val	Ile	Gly	Val	Leu	Leu	Ser	Gly	Arg	Arg	Cys	Gly
Tyr	Ser	Lys	Ala	Lys	Gln	Asp	Pro	Glu	Glu	Glu	Lys	Met	His	Phe	His
			580					585					590		
Asn	Gly	His	Ile	Lys	Leu	Pro	Gly	Val	Arg	Thr	Tyr	Ile	Asp	Pro	His
Thr	Tyr	Glu	Asp	Pro	Asn	Gln	Ala	Val	His	Glu	Phe	Ala	Lys	Glu	I

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690		695		700													
Ile	Val	Thr	Glu	Tyr	Met	Glu	Asn	Gly	Ser	Leu	Asp	Thr	Phe	Leu	Lys		
705					710					715					720		
Lys	Asn	Asp	Gly	Gln	Phe	Thr	Val	Ile	Gln	Leu	Val	Gly	Met	Leu	Arg		
				725					730					735			
Gly	Ile	Ser	Ala	Gly	Met	Lys	Tyr	Leu	Ser	Asp	Met	Gly	Tyr	Val	His		
			740					745					750				
Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Ile	Asn	Ser	Asn	Leu	Val	Cys		
		755					760					765					
Lys	Val	Ser	Asp	Phe	Gly	Leu	Ser	Arg	Val	Leu	Glu	Asp	Asp	Pro	Glu		
	770					775				780							
Ala	Ala	Tyr	Thr	Thr	Arg	Gly	Gly	Lys	Ile	Pro	Ile	Arg	Trp	Thr	Ala		
785					790					795					800		
Pro	Glu	Ala	Ile	Ala	Phe	Arg	Lys	Phe	Thr	Ser	Ala	Ser	Asp	Val	Trp		
				805				810						815			
Ser	Tyr	Gly	Ile	Val	Met	Trp	Glu	Val	Ser	Tyr	Gly	Glu	Arg	Pro			
		820					825					830					
Tyr	Trp	Glu	Met	Thr	Asn	Gln	Asp	Val	Ile	Lys	Ala	Val	Glu	Glu	Gly		
		835					840					845					
Tyr	Arg	Leu	Pro	Ser	Pro	Met	Asp	Cys	Pro	Ala	Ala	Leu	Tyr	Gln	Leu		
		850				855					860						
Met	Leu	Asp	Cys	Trp	Gln	Lys	Glu	Arg	Asn	Ser	Arg	Pro	Lys	Phe	Asp		
865				870					875					880			
Glu	Ile	Val	Asn	Met	Leu	Asp	Lys	Leu	Ile	Arg	Asn	Pro	Ser	Ser	Leu		
			885					890						895			
Lys	Thr	Leu	Val	Asn	Ala	Ser	Cys	Arg	Val	Ser	Asn	Leu	Leu	Ala	Glu		
		900						905					910				
His	Ser	Pro	Leu	Gly	Ser	Gly	Ala	Tyr	Arg	Ser	Val	Gly	Glu	Trp	Leu		
		915					920					925					
Glu	Ala	Ile	Lys	Met	Gly	Arg	Tyr	Thr	Glu	Ile	Phe	Met	Glu	Asn	Gly		
	930				935						940						
Tyr	Ser	Ser	Met	Asp	Ala	Val	Ala	Gln	Val	Thr	Leu	Glu	Asp	Leu	Arg		
945				950						955				960			
Arg	Leu	Gly	Val	Thr	Leu	Val	Gly	His	Gln	Lys	Lys	Ile	Met	Asn	Ser		
				965					970					975			
Leu	Gln	Glu	Met	Lys	Val	Gln	Leu	Val	Asn	Gly	Met	Val	Pro	Leu			
		980					985						990				

&lt;210&gt; 258

&lt;211&gt; 334

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. CAB63775

&lt;309&gt; 2005-01-20

&lt;400&gt; 258

Met	Lys	Asp	Ser	Pro	Phe	Gln	Val	Thr	Lys	Leu	Tyr	Trp	Leu	Asn	Glu		
1				5					10					15			
Lys	Trp	Asp	Phe	Ile	Ala	Ser	Ala	Ser	Asp	Met	Ala	Ala	Glu	Gln	Gly		
			20					25					30				
Gln	Ile	Leu	Val	Ile	Ala	Thr	Ala	Ala	Val	Gly	Gly	Phe	Thr	Leu	Leu		
		35				40					45						
Val	Ile	Leu	Thr	Leu	Phe	Phe	Leu	Ile	Thr	Gly	Arg	Cys	Gln	Trp	Tyr		

	50					55					60				
Ile	Lys	Ala	Lys	Met	Lys	Ser	Glu	Glu	Lys	Arg	Arg	Asn	His	Leu	Gln
65					70					75					80
Asn	Gly	His	Leu	Arg	Phe	Pro	Gly	Ile	Lys	Thr	Tyr	Ile	Asp	Pro	Asp
				85					90					95	
Thr	Tyr	Glu	Asp	Pro	Ser	Leu	Ala	Val	His	Glu	Phe	Ala	Lys	Glu	Ile
			100					105					110		
Asp	Pro	Ser	Arg	Ile	Arg	Ile	Glu	Arg	Val	Ile	Gly	Ala	Gly	Glu	Phe
			115					120				125			
Gly	Glu	Val	Cys	Ser	Gly	Arg	Leu	Lys	Thr	Pro	Gly	Lys	Arg	Glu	Ile
			130				135				140				
Pro	Val	Ala	Ile	Lys	Thr	Leu	Lys	Gly	Gly	His	Met	Asp	Arg	Gln	Arg
145					150					155					160
Arg	Asp	Phe	Leu	Arg	Glu	Ala	Ser	Ile	Met	Gly	Gln	Phe	Asp	His	Pro
				165					170					175	
Asn	Ile	Ile	Arg	Leu	Glu	Gly	Val	Val	Thr	Lys	Arg	Ser	Phe	Pro	Ala
			180					185					190		
Ile	Gly	Val	Glu	Ala	Phe	Cys	Pro	Ser	Phe	Leu	Arg	Ala	Gly	Phe	Leu
			195				200					205			
Asn	Ser	Ile	Gln	Ala	Pro	His	Pro	Val	Pro	Gly	Gly	Gly	Ser	Leu	Pro
					210		215				220				
Pro	Arg	Ile	Pro	Ala	Gly	Arg	Pro	Val	Met	Ile	Val	Val	Glu	Tyr	Met
225					230					235					240
Glu	Asn	Gly	Ser	Leu	Asp	Ser	Phe	Leu	Arg	Lys	His	Asp	Gly	His	Phe
				245					250					255	
Thr	Val	Ile	Gln	Leu	Val	Gly	Met	Leu	Arg	Gly	Ile	Ala	Ser	Gly	Met
			260					265					270		
Lys	Tyr	Leu	Ser	Asp	Met	Gly	Tyr	Val	His	Arg	Asp	Leu	Ala	Ala	Arg
			275				280					285			
Asn	Ile	Leu	Val	Asn	Ser	Asn	Leu	Val	Cys	Lys	Val	Ser	Asp	Phe	Gly
					290		295				300				
Leu	Ser	Arg	Val	Leu	Glu	Asp	Asp	Pro	Glu	Ala	Ala	Tyr	Thr	Thr	Thr
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Asp	Leu	Phe	Gln	Thr	Leu	Thr	Leu	Asn	Leu	Cys	Tyr	Ser	Ala		
				325					330						

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<309> 2005-01-26

<400> 259															
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1				5					10					15	
Trp	Leu	Leu	Arg	Phe	Ala	His	Thr	Gly	Glu	Ala	Gln	Ala	Ala	Lys	Glu
			20					25					30		
Val	Leu	Leu	Leu	Asp	Ser	Lys	Ala	Gln	Gln	Thr	Glu	Leu	Glu	Trp	Ile
			35				40					45			
Ser	Ser	Pro	Pro	Asn	Gly	Trp	Glu	Glu	Ile	Ser	Gly	Leu	Asp	Glu	Asn
	50					55					60				
Tyr	Thr	Pro	Ile	Arg	Thr	Tyr	Gln	Val	Cys	Gln	Val	Met	Glu	Pro	Asn

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65					70					75					80
Gln	Asn	Asn	Trp	Leu	Arg	Thr	Asn	Trp	Ile	Ser	Lys	Gly	Asn	Ala	Gln
				85					90					95	
Arg	Ile	Phe	Val	Glu	Leu	Lys	Phe	Thr	Leu	Arg	Asp	Cys	Asn	Ser	Leu
			100					105					110		
Pro	Gly	Val	Leu	Gly	Thr	Cys	Lys	Glu	Thr	Phe	Asn	Leu	Tyr	Tyr	Tyr
		115					120					125			
Glu	Thr	Asp	Tyr	Asp	Thr	Gly	Arg	Asn	Ile	Arg	Glu	Asn	Leu	Tyr	Val
	130					135					140				
Lys	Ile	Asp	Thr	Ile	Ala	Ala	Asp	Glu	Ser	Phe	Thr	Gln	Gly	Asp	Leu
145					150					155					160
Gly	Glu	Arg	Lys	Met	Lys	Leu	Asn	Thr	Glu	Val	Arg	Glu	Ile	Gly	Pro
			165						170					175	
Leu	Ser	Lys	Lys	Gly	Phe	Tyr	Leu	Ala	Phe	Gln	Asp	Val	Gly	Ala	Cys
			180					185					190		
Ile	Ala	Leu	Val	Ser	Val	Lys	Val	Tyr	Tyr	Lys	Lys	Cys	Trp	Ser	Ile
		195					200					205			
Ile	Glu	Asn	Leu	Ala	Ile	Phe	Pro	Asp	Thr	Val	Thr	Gly	Ser	Glu	Phe
	210					215						220			
Ser	Ser	Leu	Val	Glu	Val	Arg	Gly	Thr	Cys	Val	Ser	Ser	Ala	Glu	Glu
225					230					235					240
Glu	Ala	Glu	Asn	Ala	Pro	Arg	Met	His	Cys	Ser	Ala	Glu	Gly	Glu	Trp
			245						250					255	
Leu	Val	Pro	Ile	Gly	Lys	Cys	Ile	Cys	Lys	Ala	Gly	Tyr	Gln	Gln	Lys
			260					265						270	
Gly	Asp	Thr	Cys	Glu	Pro	Cys	Gly	Arg	Gly	Phe	Tyr	Lys	Ser	Ser	Ser
	275						280					285			
Gln	Asp	Leu	Gln	Cys	Ser	Arg	Cys	Pro	Thr	His	Ser	Phe	Ser	Asp	Lys
	290					295					300				
Glu	Gly	Ser	Ser	Arg	Cys	Glu	Cys	Glu	Asp	Gly	Tyr	Tyr	Arg	Ala	Pro
305					310					315					320
Ser	Asp	Pro	Pro	Tyr	Val	Ala	Cys	Thr	Arg	Pro	Pro	Ser	Ala	Pro	Gln
			325						330					335	
Asn	Leu	Ile	Phe	Asn	Ile	Asn	Gln	Thr	Thr	Val	Ser	Leu	Glu	Trp	Ser
			340					345					350		
Pro	Pro	Ala	Asp	Asn	Gly	Gly	Arg	Asn	Asp	Val	Thr	Tyr	Arg	Ile	Leu
		355					360					365			
Cys	Lys	Arg	Cys	Ser	Trp	Glu	Gln	Gly	Glu	Cys	Val	Pro	Cys	Gly	Ser
	370					375					380				
Asn	Ile	Gly	Tyr	Met	Pro	Gln	Gln	Thr	Gly	Leu	Glu	Asp	Asn	Tyr	Val
385					390					395					400
Thr	Val	Met	Asp	Leu	Leu	Ala	His	Ala	Asn	Tyr	Thr	Phe	Glu	Val	Glu
			405						410					415	
Ala	Val	Asn	Gly	Val	Ser	Asp	Leu	Ser	Arg	Ser	Gln	Arg	Leu	Phe	Ala
			420					425					430		
Ala	Val	Ser	Ile	Thr	Thr	Gly	Gln	Ala	Ala	Pro	Ser	Gln	Val	Ser	Gly
		435					440					445			
Val	Met	Lys	Glu	Arg	Val	Leu	Gln	Arg	Ser	Val	Glu	Leu	Ser	Trp	Gln
	450					455					460				
Glu	Pro	Glu	His	Pro	Asn	Gly	Val	Ile	Thr	Glu	Tyr	Glu	Ile	Lys	Tyr
465					470					475					480
Tyr	Glu	Lys	Asp	Gln	Arg	Glu	Arg	Thr	Tyr	Ser	Thr	Val	Lys	Thr	Lys
			485						490					495	
Ser	Thr	Ser	Ala	Ser	Ile	Asn	Asn	Leu	Lys	Pro	Gly	Thr	Val	Tyr	Val
			500					505					510		
Phe	Gln	Ile	Arg	Ala	Phe	Thr	Ala	Ala	Gly	Tyr	Gly	Asn	Tyr	Ser	Pro



[illegible]

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				965					970					975					
Ile	Met	Ser	Ser	Ile	Gln	Thr	Met	Arg	Ala	Gln	Met	Leu	His	Leu	His				
			980					985					990						
Gly	Thr	Gly	Ile	Gln	Val														
			995																

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 <212> PRT  
 <213> Homo sapiens

<300>  
 <308> GenBank No. NP065387  
 <309> 2004-11-16

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 20 25 30  
 Asn Leu Leu Asp Thr Ser Thr Ile His Gly Asp Trp Gly Trp Leu Thr  
 35 40 45  
 Tyr Pro Ala His Gly Trp Asp Ser Ile Asn Glu Val Asp Glu Ser Phe  
 50 55 60  
 Gln Pro Ile His Thr Tyr Gln Val Cys Asn Val Met Ser Pro Asn Gln  
 65 70 75 80  
 Asn Asn Trp Leu Arg Thr Ser Trp Val Pro Arg Asp Gly Ala Arg Arg  
 85 90 95  
 Val Tyr Ala Glu Ile Lys Phe Thr Leu Arg Asp Cys Asn Ser Met Pro  
 100 105 110  
 Gly Val Leu Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Leu Glu  
 115 120 125  
 Ser Asp Arg Asp Leu Gly Ala Ser Thr Gln Glu Ser Gln Phe Leu Lys  
 130 135 140  
 Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr Gly Ala Asp Leu Gly  
 145 150 155 160  
 Val Arg Arg Leu Lys Leu Asn Thr Glu Val Arg Ser Val Gly Pro Leu  
 165 170 175  
 Ser Lys Arg Gly Phe Tyr Leu Ala Phe Gln Asp Ile Gly Ala Cys Leu  
 180 185 190  
 Ala Ile Leu Ser Leu Arg Ile Tyr Tyr Lys Lys Cys Pro Ala Met Val  
 195 200 205  
 Arg Asn Leu Ala Ala Phe Ser Glu Ala Val Thr Gly Ala Asp Ser Ser  
 210 215 220  
 Ser Leu Val Glu Val Arg Gly Gln Cys Val Arg His Ser Glu Glu Arg  
 225 230 235 240  
 Asp Thr Pro Lys Met Tyr Cys Ser Ala Glu Gly Glu Trp Leu Val Pro  
 245 250 255  
 Ile Gly Lys Cys Val Cys Ser Ala Gly Tyr Glu Glu Arg Arg Asp Ala  
 260 265 270  
 Cys Val Ala Cys Glu Leu Gly Phe Tyr Lys Ser Ala Pro Gly Asp Gln  
 275 280 285  
 Leu Cys Ala Arg Cys Pro Pro His Ser His Ser Ala Ala Pro Ala Ala  
 290 295 300  
 Gln Ala Cys His Cys Asp Leu Ser Tyr Tyr Arg Ala Ala Leu Asp Pro

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305					310					315				320
Pro	Ser	Ser	Ala	Cys	Thr	Arg	Pro	Pro	Ser	Ala	Pro	Val	Asn	Leu Ile
				325					330					335
Ser	Ser	Val	Asn	Gly	Thr	Ser	Val	Thr	Leu	Glu	Trp	Ala	Pro	Pro Leu
			340					345					350	
Asp	Pro	Gly	Gly	Arg	Ser	Asp	Ile	Thr	Tyr	Asn	Ala	Val	Cys	Arg Arg
		355					360					365		
Cys	Pro	Trp	Ala	Leu	Ser	Arg	Cys	Glu	Ala	Cys	Gly	Ser	Gly	Thr Arg
		370				375					380			
Phe	Val	Pro	Gln	Gln	Thr	Ser	Leu	Val	Gln	Ala	Ser	Leu	Leu	Val Ala
385					390				395					400
Asn	Leu	Leu	Ala	His	Met	Asn	Tyr	Ser	Phe	Trp	Ile	Glu	Ala	Val Asn
				405					410					415
Gly	Val	Ser	Asp	Leu	Ser	Pro	Glu	Pro	Arg	Arg	Ala	Ala	Val	Val Asn
			420					425					430	
Ile	Thr	Thr	Asn	Gln	Ala	Ala	Pro	Ser	Gln	Val	Val	Val	Ile	Arg Gln
		435					440					445		
Glu	Arg	Ala	Gly	Gln	Thr	Ser	Val	Ser	Leu	Leu	Trp	Gln	Glu	Pro Glu
	450				455				460					
Gln	Pro	Asn	Gly	Ile	Ile	Leu	Glu	Tyr	Glu	Ile	Lys	Tyr	Tyr	Glu Lys
465				470					475					480
Asp	Lys	Glu	Met	Gln	Ser	Tyr	Ser	Thr	Leu	Lys	Ala	Val	Thr	Thr Arg
			485					490					495	
Ala	Thr	Val	Ser	Gly	Leu	Lys	Pro	Gly	Thr	Arg	Tyr	Val	Phe	Gln Val
		500						505					510	
Arg	Ala	Arg	Thr	Ser	Ala	Gly	Cys	Gly	Arg	Phe	Ser	Gln	Ala	Met Glu
	515						520					525		
Val	Glu	Thr	Gly	Lys	Pro	Arg	Pro	Arg	Tyr	Asp	Thr	Arg	Thr	Ile Val
	530				535					540				
Trp	Ile	Cys	Leu	Thr	Leu	Ile	Thr	Gly	Leu	Val	Val	Leu	Leu	Leu Leu
545					550				555					560
Leu	Ile	Cys	Lys	Lys	Arg	His	Cys	Gly	Tyr	Ser	Lys	Ala	Phe	Gln Asp
			565					570					575	
Ser	Asp	Glu	Glu	Lys	Met	His	Tyr	Gln	Asn	Gly	Gln	Ala	Pro	Pro Pro
		580						585					590	
Val	Phe	Leu	Pro	Leu	His	His	Pro	Pro	Gly	Lys	Leu	Pro	Glu	Pro Gln
	595						600					605		
Phe	Tyr	Ala	Glu	Pro	His	Thr	Tyr	Glu	Glu	Pro	Gly	Arg	Ala	Gly Arg
	610				615					620				
Ser	Phe	Thr	Arg	Glu	Ile	Glu	Ala	Ser	Arg	Ile	His	Ile	Glu	Lys Ile
625				630					635					640
Ile	Gly	Ser	Gly	Asp	Ser	Gly	Glu	Val	Cys	Tyr	Gly	Arg	Leu	Arg Val
			645					650					655	
Pro	Gly	Gln	Arg	Asp	Val	Pro	Val	Ala	Ile	Lys	Ala	Leu	Lys	Ala Gly
		660					665					670		
Tyr	Thr	Glu	Arg	Gln	Arg	Arg	Asp	Phe	Leu	Ser	Glu	Ala	Ser	Ile Met
	675						680				685			
Gly	Gln	Phe	Asp	His	Pro	Asn	Ile	Ile	Arg	Leu	Glu	Gly	Val	Val Thr
	690				695				700					
Arg	Gly	Arg	Leu	Ala	Met	Ile	Val	Thr	Glu	Tyr	Met	Glu	Asn	Gly Ser
705				710					715					720
Leu	Asp	Thr	Phe	Leu	Arg	Thr	His	Asp	Gly	Gln	Phe	Thr	Ile	Met Gln
			725					730					735	
Leu	Val	Gly	Met	Leu	Arg	Gly	Val	Gly	Ala	Gly	Met	Arg	Tyr	Leu Ser
		740					745					750		
Asp	Leu	Gly	Tyr	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Val	Leu Val

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755	760	765
Asp Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val		
770	775	780
Leu Glu Asp Asp Pro Asp Ala Ala Tyr Thr Thr Thr Gly Gly Lys Ile		
785	790	795
Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Ala Phe Arg Thr Phe Ser		800
	805	810
Ser Ala Ser Asp Val Trp Ser Phe Gly Val Val Met Trp Glu Val Leu		815
	820	825
Ala Tyr Gly Glu Arg Pro Tyr Trp Asn Met Thr Asn Arg Asp Val Ile		830
	835	840
Ser Ser Val Glu Glu Gly Tyr Arg Leu Pro Ala Pro Met Gly Cys Pro		845
	850	855
His Ala Leu His Gln Leu Met Leu Asp Cys Trp His Lys Asp Arg Ala		860
865	870	875
Gln Arg Pro Arg Phe Ser Gln Ile Val Ser Val Leu Asp Ala Leu Ile		880
	885	890
Arg Ser Pro Glu Ser Leu Arg Ala Thr Ala Thr Val Ser Arg Cys Pro		895
	900	905
Pro Pro Ala Phe Val Arg Ser Cys Phe Asp Leu Arg Gly Gly Ser Gly		910
	915	920
Gly Gly Gly Gly Leu Thr Val Gly Asp Trp Leu Asp Ser Ile Arg Met		925
	930	935
Gly Arg Tyr Arg Asp His Phe Ala Ala Gly Gly Tyr Ser Ser Leu Gly		940
945	950	955
Met Val Leu Arg Met Asn Ala Gln Asp Val Arg Ala Leu Gly Ile Thr		960
	965	970
Leu Met Gly His Gln Lys Lys Ile Leu Gly Ser Ile Gln Thr Met Arg		975
	980	985
Ala Gln Leu Thr Ser Thr Gln Gly Pro Arg Arg His Leu		990
	995	1000
		1005

&lt;210&gt; 261

&lt;211&gt; 984

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. NP004432

&lt;309&gt; 2004-11-15

&lt;400&gt; 261

Met Ala Leu Asp Tyr Leu Leu Leu Leu Leu Leu Ala Ser Ala Val Ala	
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Ala Met Glu Glu Thr Leu Met Asp Thr Arg Thr Ala Thr Ala Glu Leu	
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	15
	20
Gly Trp Thr Ala Asn Pro Ala Ser Gly Trp Glu Glu Val Ser Gly Tyr	
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	30
	35
Asp Glu Asn Leu Asn Thr Ile Arg Thr Tyr Gln Val Cys Asn Val Phe	
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	45
	50
Glu Pro Asn Gln Asn Asn Trp Leu Leu Thr Thr Phe Ile Asn Arg Arg	
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	60
65	70
Gly Ala His Arg Ile Tyr Thr Glu Met Arg Phe Thr Val Arg Asp Cys	
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	80
	85
	90
Ser Ser Leu Pro Asn Val Pro Gly Ser Cys Lys Glu Thr Phe Asn Leu	
	95

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			100					105				110			
Tyr	Tyr	Tyr	Glu	Thr	Asp	Ser	Val	Ile	Ala	Thr	Lys	Lys	Ser	Ala	Phe
		115					120					125			
Trp	Ser	Glu	Ala	Pro	Tyr	Leu	Lys	Val	Asp	Thr	Ile	Ala	Ala	Asp	Glu
		130				135					140				
Ser	Phe	Ser	Gln	Val	Asp	Phe	Gly	Gly	Arg	Leu	Met	Lys	Val	Asn	Thr
145					150				155						160
Glu	Val	Arg	Ser	Phe	Gly	Pro	Leu	Thr	Arg	Asn	Gly	Phe	Tyr	Leu	Ala
				165					170					175	
Phe	Gln	Asp	Tyr	Gly	Ala	Cys	Met	Ser	Leu	Leu	Ser	Val	Arg	Val	Phe
			180					185					190		
Phe	Lys	Lys	Cys	Pro	Ser	Ile	Val	Gln	Asn	Phe	Ala	Val	Phe	Pro	Glu
		195					200					205			
Thr	Met	Thr	Gly	Ala	Glu	Ser	Thr	Ser	Leu	Val	Ile	Ala	Arg	Gly	Thr
		210				215					220				
Cys	Ile	Pro	Asn	Ala	Glu	Glu	Val	Asp	Val	Pro	Ile	Lys	Leu	Tyr	Cys
225					230					235					240
Asn	Gly	Asp	Gly	Glu	Trp	Met	Val	Pro	Ile	Gly	Arg	Cys	Thr	Cys	Lys
				245					250					255	
Pro	Gly	Tyr	Glu	Pro	Glu	Asn	Ser	Val	Ala	Cys	Lys	Ala	Cys	Pro	Ala
			260					265					270		
Gly	Thr	Phe	Lys	Ala	Ser	Gln	Glu	Ala	Glu	Gly	Cys	Ser	His	Cys	Pro
		275					280					285			
Ser	Asn	Ser	Arg	Ser	Pro	Ala	Glu	Ala	Ser	Pro	Ile	Cys	Thr	Cys	Arg
		290				295					300				
Thr	Gly	Tyr	Tyr	Arg	Ala	Asp	Phe	Asp	Pro	Pro	Glu	Val	Ala	Cys	Thr
305					310					315					320
Ser	Val	Pro	Ser	Gly	Pro	Arg	Asn	Val	Ile	Ser	Ile	Val	Asn	Glu	Thr
				325					330					335	
Ser	Ile	Ile	Leu	Glu	Trp	His	Pro	Pro	Arg	Glu	Thr	Gly	Gly	Arg	Asp
			340					345					350		
Asp	Val	Thr	Tyr	Asn	Ile	Ile	Cys	Lys	Lys	Cys	Arg	Ala	Asp	Arg	Arg
		355					360					365			
Ser	Cys	Ser	Arg	Cys	Asp	Asp	Asn	Val	Glu	Phe	Val	Pro	Arg	Gln	Leu
		370				375					380				
Gly	Leu	Thr	Glu	Cys	Arg	Val	Ser	Ile	Ser	Ser	Leu	Trp	Ala	His	Thr
385					390					395					400
Pro	Tyr	Thr	Phe	Asp	Ile	Gln	Ala	Ile	Asn	Gly	Val	Ser	Ser	Lys	Ser
				405					410					415	
Pro	Phe	Pro	Pro	Gln	His	Val	Ser	Val	Asn	Ile	Thr	Thr	Asn	Gln	Ala
			420					425					430		
Ala	Pro	Ser	Thr	Val	Pro	Ile	Met	His	Gln	Val	Ser	Ala	Thr	Met	Arg
		435					440					445			
Ser	Ile	Thr	Leu	Ser	Trp	Pro	Gln	Pro	Glu	Gln	Pro	Asn	Gly	Ile	Ile
		450				455					460				
Leu	Asp	Tyr	Glu	Ile	Arg	Tyr	Tyr	Glu	Lys	Glu	His	Asn	Glu	Phe	Asn
465					470					475					480
Ser	Ser	Met	Ala	Arg	Ser	Gln	Thr	Asn	Thr	Ala	Arg	Ile	Asp	Gly	Leu
				485					490					495	
Arg	Pro	Gly	Met	Val	Tyr	Val	Val	Gln	Val	Arg	Ala	Arg	Thr	Val	Ala
			500					505					510		
Gly	Tyr	Gly	Lys	Phe	Ser	Gly	Lys	Met	Cys	Phe	Gln	Thr	Leu	Thr	Asp
		515					520					525			
Asp	Asp	Tyr	Lys	Ser	Glu	Leu	Arg	Glu	Gln	Leu	Pro	Leu	Ile	Ala	Gly
		530				535					540				
Ser	Ala	Ala	Ala	Gly	Val	Val	Phe	Val	Val	Ser	Leu	Val	Ala	Ile	Ser

545					550					555					560
Ile	Val	Cys	Ser	Arg	Lys	Arg	Ala	Tyr	Ser	Lys	Glu	Ala	Val	Tyr	Ser
				565					570					575	
Asp	Lys	Leu	Gln	His	Tyr	Ser	Thr	Gly	Arg	Gly	Ser	Pro	Gly	Met	Lys
			580					585					590		
Ile	Tyr	Ile	Asp	Pro	Phe	Thr	Tyr	Glu	Asp	Pro	Asn	Glu	Ala	Val	Arg
		595					600				605				
Glu	Phe	Ala	Lys	Glu	Ile	Asp	Val	Ser	Phe	Val	Lys	Ile	Glu	Glu	Val
	610					615					620				
Ile	Gly	Ala	Gly	Glu	Phe	Gly	Glu	Val	Tyr	Lys	Gly	Arg	Leu	Lys	Leu
625					630					635					640
Pro	Gly	Lys	Arg	Glu	Ile	Tyr	Val	Ala	Ile	Lys	Thr	Leu	Lys	Ala	Gly
			645						650					655	
Tyr	Ser	Glu	Lys	Gln	Arg	Arg	Asp	Phe	Leu	Ser	Glu	Ala	Ser	Ile	Met
			660					665					670		
Gly	Gln	Phe	Asp	His	Pro	Asn	Ile	Ile	Arg	Leu	Glu	Gly	Val	Val	Thr
		675					680					685			
Lys	Ser	Arg	Pro	Val	Met	Ile	Ile	Thr	Glu	Phe	Met	Glu	Asn	Gly	Ala
		690				695					700				
Leu	Asp	Ser	Phe	Leu	Arg	Gln	Asn	Asp	Gly	Gln	Phe	Thr	Val	Ile	Gln
705					710					715					720
Leu	Val	Gly	Met	Leu	Arg	Gly	Ile	Ala	Ala	Gly	Met	Lys	Tyr	Leu	Ala
			725						730					735	
Glu	Met	Asn	Tyr	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Val
			740					745					750		
Asn	Ser	Asn	Leu	Val	Cys	Lys	Val	Ser	Asp	Phe	Gly	Leu	Ser	Arg	Tyr
		755					760					765			
Leu	Gln	Asp	Asp	Thr	Ser	Asp	Pro	Thr	Tyr	Thr	Ser	Ser	Leu	Gly	Gly
		770				775						780			
Lys	Ile	Pro	Val	Arg	Trp	Thr	Ala	Pro	Glu	Ala	Ile	Ala	Tyr	Arg	Lys
785					790					795					800
Phe	Thr	Ser	Ala	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Ile	Val	Met	Trp	Glu
			805						810					815	
Val	Met	Ser	Phe	Gly	Glu	Arg	Pro	Tyr	Trp	Asp	Met	Ser	Asn	Gln	Asp
			820					825					830		
Val	Ile	Asn	Ala	Ile	Glu	Gln	Asp	Tyr	Arg	Leu	Pro	Pro	Pro	Met	Asp
		835					840					845			
Cys	Pro	Ala	Ala	Leu	His	Gln	Leu	Met	Leu	Asp	Cys	Trp	Gln	Lys	Asp
		850				855					860				
Arg	Asn	Ser	Arg	Pro	Arg	Phe	Ala	Glu	Ile	Val	Asn	Thr	Leu	Asp	Lys
865					870					875					880
Met	Ile	Arg	Asn	Pro	Ala	Ser	Leu	Lys	Thr	Val	Ala	Thr	Ile	Thr	Ala
			885						890					895	
Val	Pro	Ser	Gln	Pro	Leu	Leu	Asp	Arg	Ser	Ile	Pro	Asp	Phe	Thr	Ala
			900												

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<210> 262  
 <211> 1055  
 <212> PRT  
 <213> Homo sapiens

<300>  
 <308> GenBank No. AAB94602  
 <309> 2000-11-29

<400> 262  
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 35 40 45  
 Tyr Asp Glu Asn Met Asn Thr Ile Arg Thr Tyr Gln Val Cys Asn Val  
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 Phe Glu Ser Ser Gln Asn Trp Leu Arg Thr Lys Phe Ile Arg Arg  
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 Arg Gly Ala His Arg Ile His Val Glu Met Lys Phe Ser Val Arg Asp  
 85 90 95  
 Cys Ser Ser Ile Pro Ser Val Pro Gly Ser Cys Lys Glu Thr Phe Asn  
 100 105 110  
 Leu Tyr Tyr Tyr Glu Ala Asp Phe Asp Ser Ala Thr Lys Thr Phe Pro  
 115 120 125  
 Asn Trp Met Glu Asn Pro Trp Val Lys Val Asp Thr Ile Ala Ala Asp  
 130 135 140  
 Glu Ser Phe Ser Gln Val Asp Leu Gly Gly Arg Val Met Lys Ile Asn  
 145 150 155 160  
 Thr Glu Val Arg Ser Phe Gly Pro Val Ser Arg Ser Gly Phe Tyr Leu  
 165 170 175  
 Ala Phe Gln Asp Tyr Gly Gly Cys Met Ser Leu Ile Ala Val Arg Val  
 180 185 190  
 Phe Tyr Arg Lys Cys Pro Arg Ile Ile Gln Asn Gly Ala Ile Phe Gln  
 195 200 205  
 Glu Thr Leu Ser Gly Ala Glu Ser Thr Ser Leu Val Ala Ala Arg Gly  
 210 215 220  
 Ser Cys Ile Ala Asn Ala Glu Glu Val Asp Val Pro Ile Lys Leu Tyr  
 225 230 235 240  
 Cys Asn Gly Asp Gly Glu Trp Leu Val Pro Ile Gly Arg Cys Met Cys  
 245 250 255  
 Lys Ala Gly Phe Glu Ala Val Glu Asn Gly Thr Val Cys Arg Gly Cys  
 260 265 270  
 Pro Ser Gly Thr Phe Lys Ala Asn Gln Gly Asp Glu Ala Cys Thr His  
 275 280 285  
 Cys Pro Ile Asn Ser Arg Thr Thr Ser Glu Gly Ala Thr Asn Cys Val  
 290 295 300  
 Cys Arg Asn Gly Tyr Tyr Arg Ala Asp Leu Asp Pro Leu Asp Met Pro  
 305 310 315 320  
 Cys Thr Thr Ile Pro Ser Ala Pro Gln Ala Val Ile Ser Ser Val Asn  
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 Glu Thr Ser Leu Met Leu Glu Trp Thr Pro Pro Arg Asp Ser Gly Gly  
 340 345 350  
 Arg Glu Asp Leu Val Tyr Asn Ile Ile Cys Lys Ser Cys Gly Ser Gly

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Gln	Leu	Gly	Leu	Thr	Glu	Pro	Arg	Ile	Tyr	Ile	Ser	Asp	Leu	Leu	Ala		
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His	Thr	Gln	Tyr	Thr	Phe	Glu	Ile	Gln	Ala	Val	Asn	Gly	Val	Thr	Asp		
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Tyr	Asn	Ala	Thr	Ala	Ile	Lys	Ser	Pro	Thr	Asn	Thr	Val	Thr	Val	Gln		
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Gly	Leu	Lys	Ala	Gly	Ala	Ile	Tyr	Val	Phe	Gln	Val	Arg	Ala	Arg	Thr		
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Thr	Glu	Ala	Glu	Tyr	Gln	Thr	Ser	Ile	Gln	Glu	Lys	Leu	Pro	Leu	Ile		
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Ile	Gly	Ser	Ser	Ala	Ala	Gly	Leu	Val	Phe	Leu	Ile	Ala	Val	Val	Val		
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Ile	Ala	Ile	Val	Cys	Asn	Arg	Arg	Gly	Phe	Glu	Arg	Ala	Asp	Ser	Glu		
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Lys	Leu	Pro	Gly	Lys	Arg	Glu	Ile	Phe	Val	Ala	Ile	Lys	Thr	Leu	Lys		
				645					650					655			
Ser	Gly	Tyr	Thr	Glu	Lys	Gln	Arg	Arg	Asp	Phe	Leu	Ser	Glu	Ala	Ser		
			660					665					670				
Ile	Met	Gly	Gln	Phe	Asp	His	Pro	Asn	Val	Ile	His	Leu	Glu	Gly	Val		
	675						680					685					
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	690					695					700						
Gly	Ser	Leu	Asp	Ser	Phe	Leu	Arg	Gln	Asn	Asp	Gly	Gln	Phe	Thr	Val		
705					710					715							



				805						810						815		
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Gln	Asp	Val	Ile	Asn	Ala	Ile	Glu	Gln	Asp	Tyr	Arg	Leu	Pro	Pro	Pro			
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Met	Asp	Cys	Pro	Ser	Ala	Leu	His	Gln	Leu	Met	Leu	Asp	Cys	Trp	Gln			
	850					855				860								
Lys	Asp	Arg	Asn	His	Arg	Pro	Lys	Phe	Gly	Gln	Ile	Val	Asn	Thr	Leu			
865					870					875					880			
Asp	Lys	Met	Ile	Arg	Asn	Pro	Asn	Ser	Leu	Lys	Ala	Met	Ala	Pro	Leu			
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Ser	Ser	Gly	Ile	Asn	Leu	Pro	Leu	Leu	Asp	Arg	Thr	Ile	Pro	Asp	Tyr			
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Thr	Ser	Phe	Asn	Thr	Val	Asp	Glu	Trp	Leu	Glu	Ala	Ile	Lys	Met	Gly			
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Ala	Gly	His	Gln	Lys	Lys	Ile	Leu	Asn	Ser	Ile	Gln	Val	Met	Arg	Ala			
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Gln	Met	Asn	Gln	Ile	Gln	Ser	Val	Glu	Gly	Gln	Pro	Leu	Ala	Arg	Arg			
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Pro	Arg	Ala	Thr	Gly	Arg	Thr	Lys	Arg	Cys	Gln	Pro	Arg	Asp	Val	Thr			
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Lys	Lys	Thr	Cys	Asn	Ser	Asn	Asp	Gly	Lys	Lys	Lys	Gly	Met	Gly	Lys			
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Lys	Lys	Thr	Asp	Pro	Gly	Arg	Gly	Arg	Glu	Ile	Gln	Gly	Ile	Phe	Phe			
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<211> 998
<212> PRT
<213> Homo sapiens
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<308> GenBank No. NP004434  
<309> 2004-11-16

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Cys	Asn	Val	Arg	Glu	Ser	Ser	Gln	Asn	Asn	Trp	Leu	Arg	Thr	Gly	Phe	
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Lys	Val	Arg	Ser	Phe	Gly	Pro	Leu	Ser	Lys	Ala	Gly	Phe	Tyr	Leu	Ala		
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Tyr	Lys	Lys	Cys	Ala	Ser	Thr	Thr	Ala	Gly	Phe	Ala	Leu	Phe	Pro	Glu		
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Thr	Leu	Thr	Gly	Ala	Glu	Pro	Thr	Ser	Leu	Val	Ile	Ala	Pro	Gly	Thr		
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Cys	Ile	Pro	Asn	Ala	Val	Glu	Val	Ser	Val	Pro	Leu	Lys	Leu	Tyr	Cys		
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Pro	Gly	Ser	Tyr	Lys	Ala	Lys	Gln	Gly	Glu	Gly	Pro	Cys	Leu	Pro	Cys		
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Pro	Pro	Asn	Ser	Arg	Thr	Thr	Ser	Pro	Ala	Ala	Ser	Ile	Cys	Thr	Cys		
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His	Asn	Asn	Phe	Tyr	Arg	Ala	Asp	Ser	Asp	Ser	Ala	Asp	Ser	Ala	Cys		
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Thr	Thr	Val	Pro	Ser	Pro	Pro	Arg	Gly	Val	Ile	Ser	Asn	Val	Asn	Glu		
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Thr	Ser	Leu	Ile	Leu	Glu	Trp	Ser	Glu	Pro	Arg	Asp	Leu	Gly	Gly	Arg		
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Asp	Asp	Leu	Leu	Tyr	Asn	Val	Ile	Cys	Lys	Lys	Cys	His	Gly	Ala	Gly		
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Gly	Ala	Ser	Ala	Cys	Ser	Arg	Cys	Asp	Asp	Asn	Val	Glu	Phe	Val	Pro		
385				390					395						400		
Arg	Gln	Leu	Gly	Leu	Thr	Glu	Arg	Arg	Val	His	Ile	Ser	His	Leu	Leu		
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Ala	His	Thr	Arg	Tyr	Thr	Phe	Glu	Val	Gln	Ala	Val	Asn	Gly	Val	Ser		
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		450				455					460						
Ser	Gly	Ser	Ser	Leu	Thr	Leu	Ser	Trp	Ala	Pro	Pro	Glu	Arg	Pro	Asn		
465				470					475					480			
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Ile	Ala	Ser	Thr	Val	Thr	Ser	Gln	Met	Asn	Ser	Val	Gln	Leu	Asp	Gly		
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Ile	Ala	Ile	Val	Cys	Leu	Arg	Lys	Gln	Arg	His	Gly	Ser	Asp	Ser	Glu			
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Tyr	Thr	Glu	Lys	Leu	Gln	Gln	Tyr	Ile	Ala	Pro	Gly	Met	Lys	Val	Tyr			
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Ala	Gly	Glu	Phe	Gly	Glu	Val	Cys	Arg	Gly	Arg	Leu	Lys	Gln	Pro	Gly			
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			660					665					670					
Glu	Arg	Gln	Arg	Arg	Asp	Phe	Leu	Ser	Glu	Ala	Ser	Ile	Met	Gly	Gln			
			675				680					685						
Phe	Asp	His	Pro	Asn	Ile	Ile	Arg	Leu	Glu	Gly	Val	Val	Thr	Lys	Ser			
	690					695					700							
Arg	Pro	Val	Met	Ile	Leu	Thr	Glu	Phe	Met	Glu	Asn	Cys	Ala	Leu	Asp			
705				710						715					720			
Ser	Phe	Leu	Arg	Leu	Asn	Asp	Gly	Gln	Phe	Thr	Val	Ile	Gln	Leu	Val			
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Gly	Met	Leu	Arg	Gly	Ile	Ala	Ala	Gly	Met	Lys	Tyr	Leu	Ser	Glu	Met			
			740					745					750					
Asn	Tyr	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Val	Asn	Ser			
		755				760						765						
Asn	Leu	Val	Cys	Lys	Val	Ser	Asp	Phe	Gly	Leu	Ser	Arg	Phe	Leu	Glu			
	770					775					780							
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785					790					795					800			
Pro	Ile	Arg	Trp	Thr	Ala	Pro	Glu	Ala	Ile	Ala	Tyr	Arg	Lys	Phe	Thr			
				805					810					815				
Ser	Ala	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Ile	Val	Met	Trp	Glu	Val	Met			
			820					825					830					
Ser	Tyr	Gly	Glu	Arg	Pro	Tyr	Trp	Asp	Met	Ser	Asn	Gln	Asp	Val	Ile			
		835					840					845						
Asn	Ala	Val	Glu	Gln	Asp	Tyr	Arg	Leu	Pro	Pro	Pro	Met	Asp	Cys	Pro			
	850					855						860						
Thr	Ala	Leu	His	Gln	Leu	Met	Leu	Asp	Cys	Trp	Val	Arg	Asp	Arg	Asn			
865					870					875					880			
Leu	Arg	Pro	Lys	Phe	Ser	Gln	Ile	Val	Asn	Thr	Leu	Asp	Lys	Leu	Ile			
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995

<210> 264  
 <211> 987  
 <212> PRT  
 <213> Homo sapiens

<300>  
 <308> GenBank No.NP004435  
 <309> 2004-11-16

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 Val Thr Phe Pro Gln Val Asp Gly Gln Trp Glu Glu Leu Ser Gly Leu  
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 Asp Glu Glu Gln His Ser Val Arg Thr Tyr Glu Val Cys Asp Val Gln  
 50 55 60  
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 65 70 75 80  
 Arg Gly Ala Val His Val Tyr Ala Thr Leu Arg Phe Thr Met Leu Glu  
 85 90 95  
 Cys Leu Ser Leu Pro Arg Ala Gly Arg Ser Cys Lys Glu Thr Phe Thr  
 100 105 110  
 Val Phe Tyr Tyr Glu Ser Asp Ala Asp Thr Ala Thr Ala Leu Thr Pro  
 115 120 125  
 Ala Trp Met Glu Asn Pro Tyr Ile Lys Val Asp Thr Val Ala Ala Glu  
 130 135 140  
 His Leu Thr Arg Lys Arg Pro Gly Ala Glu Ala Thr Gly Lys Val Asn  
 145 150 155 160  
 Val Lys Thr Leu Arg Leu Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu  
 165 170 175  
 Ala Phe Gln Asp Gln Gly Ala Cys Met Ala Leu Leu Ser Leu His Leu  
 180 185 190  
 Phe Tyr Lys Lys Cys Ala Gln Leu Thr Val Asn Leu Thr Arg Phe Pro  
 195 200 205  
 Glu Thr Val Pro Arg Glu Leu Val Val Pro Val Ala Gly Ser Cys Val  
 210 215 220  
 Val Asp Ala Val Pro Ala Pro Gly Pro Ser Pro Ser Leu Tyr Cys Arg  
 225 230 235 240  
 Glu Asp Gly Gln Trp Ala Glu Gln Pro Val Thr Gly Cys Ser Cys Ala  
 245 250 255  
 Pro Gly Phe Glu Ala Ala Glu Gly Asn Thr Lys Cys Arg Ala Cys Ala  
 260 265 270  
 Gln Gly Thr Phe Lys Pro Leu Ser Gly Glu Gly Ser Cys Gln Pro Cys  
 275 280 285  
 Pro Ala Asn Ser His Ser Asn Thr Ile Gly Ser Ala Val Cys Gln Cys  
 290 295 300  
 Arg Val Gly Tyr Phe Arg Ala Arg Thr Asp Pro Arg Gly Ala Pro Cys  
 305 310 315 320  
 Thr Thr Pro Pro Ser Ala Pro Arg Ser Val Val Ser Arg Leu Asn Gly  
 325 330 335  
 Ser Ser Leu His Leu Glu Trp Ser Ala Pro Leu Glu Ser Gly Gly Arg

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Ser	Cys	Ala	Pro	Cys	Gly	Gly	Asp	Leu	Thr	Phe	Asp	Pro	Gly	Pro	Arg	
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Asp	Leu	Val	Glu	Pro	Trp	Val	Val	Val	Arg	Gly	Leu	Arg	Pro	Asp	Phe	
385					390					395					400	
Thr	Tyr	Thr	Phe	Glu	Val	Thr	Ala	Leu	Asn	Gly	Val	Ser	Ser	Leu	Ala	
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Thr	Gly	Pro	Val	Pro	Phe	Glu	Pro	Val	Asn	Val	Thr	Thr	Asp	Arg	Glu	
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Val	Pro	Pro	Ala	Val	Ser	Asp	Ile	Arg	Val	Thr	Arg	Ser	Ser	Pro	Ser	
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Ser	Leu	Ser	Leu	Ala	Trp	Ala	Val	Pro	Arg	Ala	Pro	Ser	Gly	Ala	Val	
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Leu	Asp	Tyr	Glu	Val	Lys	Tyr	His	Glu	Lys	Gly	Ala	Glu	Gly	Pro	Ser	
465					470					475					480	
Ser	Val	Arg	Phe	Leu	Lys	Thr	Ser	Glu	Asn	Arg	Ala	Glu	Leu	Arg	Gly	
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Leu	Lys	Arg	Gly	Ala	Ser	Tyr	Leu	Val	Gln	Val	Arg	Ala	Arg	Ser	Glu	
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Ala	Gly	Tyr	Gly	Pro	Phe	Gly	Gln	Glu	His	His	Ser	Gln	Thr	Gln	Leu	
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Ala	Val	Val	Gly	Val	Val	Leu	Val	Leu	Val	Val	Ile	Val	Val	Ala	Val	
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Lys	His	Gly	Gln	Tyr	Leu	Ile	Gly	His	Gly	Thr	Lys	Val	Tyr	Ile	Asp	
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Glu	Ile	Asp	Val	Ser	Tyr	Val	Lys	Ile	Glu	Glu	Val	Ile	Gly	Ala	Gly	
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Gln	Arg	Arg	Glu	Phe	Leu	Ser	Glu	Ala	Ser	Ile	Met	Gly	Gln	Phe	Glu	
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His	Pro	Asn	Ile	Ile	Arg	Leu	Glu	Gly	Val	Val	Thr	Asn	Ser	Met	Pro	
		675					680					685	</			

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785              790              795              800
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              820              825              830
Ile Glu Gln Asp Tyr Arg Leu Pro Pro Pro Asp Cys Pro Thr Ser
              835              840              845
Leu His Gln Leu Met Leu Asp Cys Trp Gln Lys Asp Arg Asn Ala Arg
              850              855              860
Pro Arg Phe Pro Gln Val Val Ser Ala Leu Asp Lys Met Ile Arg Asn
865              870              875              880
Pro Ala Ser Leu Lys Ile Val Ala Arg Glu Asn Gly Gly Ala Ser His
              885              890              895
Pro Leu Leu Asp Gln Arg Gln Pro His Tyr Ser Ala Phe Gly Ser Val
              900              905              910
Gly Glu Trp Leu Arg Ala Ile Lys Met Gly Arg Tyr Glu Glu Ser Phe
              915              920              925
Ala Ala Ala Gly Phe Gly Ser Phe Glu Leu Val Ser Gln Ile Ser Ala
              930              935              940
Glu Asp Leu Leu Arg Ile Gly Val Thr Leu Ala Gly His Gln Lys Lys
945              950              955              960
Ile Leu Ala Ser Val Gln His Met Lys Ser Gln Ala Lys Pro Gly Thr
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Pro Gly Gly Thr Gly Gly Pro Ala Pro Gln Tyr
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&lt;210&gt; 265

&lt;211&gt; 1006

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank No.NP004436

&lt;309&gt; 2004-11-29

&lt;400&gt; 265

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Trp Leu Thr Tyr Pro Pro Gly Gly Trp Asp Glu Val Ser Val Leu Asp
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Asp Gln Arg Arg Leu Thr Arg Thr Phe Glu Ala Cys His Val Ala Gly
              50              55              60
Ala Pro Pro Gly Thr Gly Gln Asp Asn Trp Leu Gln Thr His Phe Val
65              70              75              80
Glu Arg Arg Gly Ala Gln Arg Ala His Ile Arg Leu His Phe Ser Val
              85              90              95
Arg Ala Cys Ser Ser Leu Gly Val Ser Gly Gly Thr Cys Arg Glu Thr
              100              105              110
Phe Thr Leu Tyr Tyr Arg Gln Ala Glu Glu Pro Asp Ser Pro Asp Ser
              115              120              125
Val Ser Ser Trp His Leu Lys Arg Trp Thr Lys Val Asp Thr Ile Ala
              130              135              140
Ala Asp Glu Ser Phe Pro Ser Ser Ser Ser Ser Ser Ser Ser Ser

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145					150					155				160
Ser	Ala	Ala	Trp	Ala	Val	Gly	Pro	His	Gly	Ala	Gly	Gln	Arg	Ala
				165					170					175
Leu	Gln	Leu	Asn	Val	Lys	Glu	Arg	Ser	Phe	Gly	Pro	Leu	Thr	Gln
			180					185					190	
Gly	Phe	Tyr	Val	Ala	Phe	Gln	Asp	Thr	Gly	Ala	Cys	Leu	Ala	Leu
		195					200					205		
Ala	Val	Arg	Leu	Phe	Ser	Tyr	Thr	Cys	Pro	Ala	Val	Leu	Arg	Ser
	210					215					220			Phe
Ala	Ser	Phe	Pro	Glu	Thr	Gln	Ala	Ser	Gly	Ala	Gly	Gly	Ala	Ser
225						230				235				240
Val	Ala	Ala	Val	Gly	Thr	Cys	Val	Ala	His	Ala	Glu	Pro	Glu	Glu
			245						250					255
Gly	Val	Gly	Gly	Gln	Ala	Gly	Gly	Ser	Pro	Pro	Arg	Leu	His	Cys
			260					265					270	Asn
Gly	Glu	Gly	Lys	Trp	Met	Val	Ala	Val	Gly	Gly	Cys	Arg	Cys	Gln
		275					280						285	Pro
Gly	Tyr	Gln	Pro	Ala	Arg	Gly	Asp	Lys	Ala	Cys	Gln	Ala	Cys	Pro
	290					295				300				Arg
Gly	Leu	Tyr	Lys	Ser	Ser	Ala	Gly	Asn	Ala	Pro	Cys	Ser	Pro	Cys
305				310						315				320
Ala	Arg	Ser	His	Ala	Pro	Asn	Pro	Ala	Ala	Pro	Val	Cys	Pro	Cys
			325						330					335
Glu	Gly	Phe	Tyr	Arg	Ala	Ser	Ser	Asp	Pro	Pro	Glu	Ala	Pro	Cys
			340					345					350	Thr
Gly	Pro	Pro	Ser	Ala	Pro	Gln	Glu	Leu	Trp	Phe	Glu	Val	Gln	Gly
		355					360					365		Ser
Ala	Leu	Met	Leu	His	Trp	Arg	Leu	Pro	Arg	Glu	Leu	Gly	Gly	Arg
	370					375				380				Gly
Asp	Leu	Leu	Phe	Asn	Val	Cys	Lys	Glu	Cys	Glu	Gly	Arg	Gln	Glu
385				390					395					400
Pro	Ala	Ser	Gly	Gly	Gly	Gly	Thr	Cys	His	Arg	Cys	Arg	Asp	Glu
			405						410					415
His	Phe	Asp	Pro	Arg	Gln	Arg	Gly	Leu	Thr	Glu	Ser	Arg	Val	Leu
			420					425					430	Val
Gly	Gly	Leu	Arg	Ala	His	Val	Pro	Tyr	Ile	Leu	Glu	Val	Gln	Ala
		435					440					445		Val
Asn	Gly	Val	Ser	Glu	Leu	Ser	Pro	Asp	Pro	Pro	Gln	Ala	Ala	Ala
	450					455				460				Ile
Asn	Val	Ser	Thr	Ser	His	Glu	Val	Pro	Ser	Ala	Val	Pro	Val	Val
465				470					475					480
Gln	Val	Ser	Arg	Ala	Ser	Asn	Ser	Ile	Thr	Val	Ser	Trp	Pro	Gln
			485						490					495
Asp	Gln	Thr	Asn	Gly	Asn	Ile	Leu	Asp	Tyr	Gln	Leu	Arg	Tyr	Tyr
		500					505					510		Asp
Gln	Ala	Glu	Asp	Glu	Ser	His	Ser	Phe	Thr	Leu	Thr	Ser	Glu	Thr
		515					520					525		Asn
Thr	Ala	Thr	Val	Thr	Gln	Leu	Ser	Pro	Gly	His	Ile	Tyr	Gly	Phe
	530					535					540			Gln
Val	Arg	Ala	Arg	Thr	Ala	Ala	Gly	His	Gly	Pro	Tyr	Gly	Gly	Lys
545					550					555				560
Tyr	Phe	Gln	Thr	Leu	Pro	Gln	Gly	Glu	Leu	Ser	Ser	Gln	Leu	Pro
			565						570					575
Arg	Leu	Ser	Leu	Val	Ile	Gly	Ser	Ile	Leu	Gly	Ala	Leu	Ala	Phe
			580					585					590	Leu
Leu	Leu	Ala	Ala	Ile	Thr	Val	Leu	Ala	Val	Val	Phe	Gln	Arg	Lys

	595					600					605					
Arg	Gly	Thr	Gly	Tyr	Thr	Glu	Gln	Leu	Gln	Gln	Tyr	Ser	Ser	Pro	Gly	
	610					615					620					
Leu	Gly	Val	Lys	Tyr	Tyr	Ile	Asp	Pro	Ser	Thr	Tyr	Glu	Asp	Pro	Cys	
625					630						635				640	
Gln	Ala	Ile	Arg	Glu	Leu	Ala	Arg	Glu	Val	Asp	Pro	Ala	Tyr	Ile	Lys	
				645						650					655	
Ile	Glu	Glu	Val	Ile	Gly	Thr	Gly	Ser	Phe	Gly	Glu	Val	Arg	Gln	Gly	
			660					665					670			
Arg	Leu	Gln	Pro	Arg	Gly	Arg	Arg	Glu	Gln	Thr	Val	Ala	Ile	Gln	Ala	
		675				680						685				
Leu	Trp	Ala	Gly	Gly	Ala	Glu	Ser	Leu	Gln	Met	Thr	Phe	Leu	Gly	Arg	
	690					695					700					
Ala	Ala	Val	Leu	Gly	Gln	Phe	Gln	His	Pro	Asn	Ile	Leu	Arg	Leu	Glu	
705					710					715					720	
Gly	Val	Val	Thr	Lys	Ser	Arg	Pro	Leu	Met	Val	Leu	Thr	Glu	Phe	Met	
				725						730					735	
Glu	Leu	Gly	Pro	Leu	Asp	Ser	Phe	Leu	Arg	Gln	Arg	Glu	Gly	Gln	Phe	
			740				745					750				
Ser	Ser	Leu	Gln	Leu	Val	Ala	Met	Gln	Arg	Gly	Val	Ala	Ala	Ala	Met	
		755					760					765				
Gln	Tyr	Leu	Ser	Ser	Phe	Ala	Phe	Val	His	Arg	Ser	Leu	Ser	Ala	His	
	770					775					780					
Ser	Val	Leu	Val	Asn	Ser	His	Leu	Val	Cys	Lys	Val	Ala	Arg	Leu	Gly	
785				790						795					800	
His	Ser	Pro	Gln	Gly	Pro	Ser	Cys	Leu	Leu	Arg	Trp	Ala	Ala	Pro	Glu	
				805						810				815		
Val	Ile	Ala	His	Gly	Lys	His	Thr	Thr	Ser	Ser	Asp	Val	Trp	Ser	Phe	
			820				825						830			
Gly	Ile	Leu	Met	Trp	Glu	Val	Met	Ser	Tyr	Gly	Glu	Arg	Pro	Tyr	Trp	
		835					840					845				
Asp	Met	Ser	Glu	Gln	Glu	Val	Leu	Asn	Ala	Ile	Glu	Gln	Glu	Phe	Arg	
	850					855					860					
Leu	Pro	Pro	Pro	Pro	Gly	Cys	Pro	Pro	Gly	Leu	His	Leu	Leu	Met	Leu	
865					870					875					880	
Asp	Thr	Trp	Gln	Lys	Asp	Arg	Ala	Arg	Arg	Pro	His	Phe	Asp	Gln	Leu	
			885						890					895		
Val	Ala	Ala	Phe	Asp	Lys	Met	Ile	Arg	Lys	Pro	Asp	Thr	Leu	Gln	Ala	
			900					905					910			
Gly	Gly	Asp	Pro	Gly	Glu	Arg	Pro	Ser	Gln	Ala	Leu	Leu	Thr	Pro	Val	
		915					920					925				
Ala	Leu	Asp	Phe	Pro	Cys	Leu	Asp	Ser	Pro	Gln	Ala	Trp	Leu	Ser	Ala	
	930					935					940					
Ile	Gly	Leu	Glu	Cys	Tyr	Gln	Asp	Asn	Phe	Ser	Lys	Phe	Gly	Leu	Cys	
945					950					955						

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<210> 266
<211> 1255
<212> PRT
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&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. NP004439

&lt;309&gt; 2004-12-20

&lt;400&gt; 266

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Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1          5          10          15
Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
      20          25          30
Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
      35          40          45
Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
      50          55          60
Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
      65          70          75          80
Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
      85          90          95
Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
      100          105          110
Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
      115          120          125
Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
      130          135          140
Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
      145          150          155          160
Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
      165          170          175
Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
      180          185          190
His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
      195          200          205
Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
      210          215          220
Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
      225          230          235          240
Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
      245          250          255
His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
      260          265          270
Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
      275          280          285
Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
      290          295          300
Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
      305          310          315          320
Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
      325          330          335
Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu
      340          345          350
Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys
      355          360          365
Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp
      370          375          380
Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe

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385					390					395				400	
Glu	Thr	Leu	Glu	Glu	Ile	Thr	Gly	Tyr	Leu	Tyr	Ile	Ser	Ala	Trp	Pro
				405					410					415	
Asp	Ser	Leu	Pro	Asp	Leu	Ser	Val	Phe	Gln	Asn	Leu	Gln	Val	Ile	Arg
			420					425					430		
Gly	Arg	Ile	Leu	His	Asn	Gly	Ala	Tyr	Ser	Leu	Thr	Leu	Gln	Gly	Leu
		435					440					445			
Gly	Ile	Ser	Trp	Leu	Gly	Leu	Arg	Ser	Leu	Arg	Glu	Leu	Gly	Ser	Gly
	450					455					460				
Leu	Ala	Leu	Ile	His	His	Asn	Thr	His	Leu	Cys	Phe	Val	His	Thr	Val
465					470					475					480
Pro	Trp	Asp	Gln	Leu	Phe	Arg	Asn	Pro	His	Gln	Ala	Leu	Leu	His	Thr
				485					490					495	
Ala	Asn	Arg	Pro	Glu	Asp	Glu	Cys	Val	Gly	Glu	Gly	Leu	Ala	Cys	His
			500					505					510		
Gln	Leu	Cys	Ala	Arg	Gly	His	Cys	Trp	Gly	Pro	Gly	Pro	Thr	Gln	Cys
		515					520					525			
Val	Asn	Cys	Ser	Gln	Phe	Leu	Arg	Gly	Gln	Glu	Cys	Val	Glu	Glu	Cys
	530					535					540				
Arg	Val	Leu	Gln	Gly	Leu	Pro	Arg	Glu	Tyr	Val	Asn	Ala	Arg	His	Cys
545					550					555					560
Leu	Pro	Cys	His	Pro	Glu	Cys	Gln	Pro	Gln	Asn	Gly	Ser	Val	Thr	Cys
				565					570					575	
Phe	Gly	Pro	Glu	Ala	Asp	Gln	Cys	Val	Ala	Cys	Ala	His	Tyr	Lys	Asp
		580						585					590		
Pro	Pro	Phe	Cys	Val	Ala	Arg	Cys	Pro	Ser	Gly	Val	Lys	Pro	Asp	Leu
		595					600					605			
Ser	Tyr	Met	Pro	Ile	Trp	Lys	Phe	Pro	Asp	Glu	Glu	Gly	Ala	Cys	Gln
		610				615					620				
Pro	Cys	Pro	Ile	Asn	Cys	Thr	His	Ser	Cys	Val	Asp	Leu	Asp	Asp	Lys
625				630						635					640
Gly	Cys	Pro	Ala	Glu	Gln	Arg	Ala	Ser	Pro	Leu	Thr	Ser	Ile	Ile	Ser
			645						650					655	
Ala	Val	Val	Gly	Ile	Leu	Leu	Val	Val	Leu	Gly	Val	Val	Val	Phe	Gly
		660					665					670			
Ile	Leu	Ile	Lys	Arg	Arg	Gln	Gln	Lys	Ile	Arg	Lys	Tyr	Thr	Met	Arg
		675				680						685			
Arg	Leu	Leu	Gln	Glu	Thr	Glu	Leu	Val	Glu	Pro	Leu	Thr	Pro	Ser	Gly
	690					695					700				
Ala	Met	Pro	Asn	Gln	Ala	Gln	Met	Arg	Ile	Leu	Lys	Glu	Thr	Glu	Leu
705				710						715					720
Arg	Lys	Val	Lys	Val	Leu	Gly	Ser	Gly	Ala	Phe	Gly	Thr	Val	Tyr	Lys
			725						730					735	
Gly	Ile	Trp	Ile	Pro	Asp	Gly	Glu	Asn	Val	Lys	Ile	Pro	Val	Ala	Ile
			740					745					750		
Lys	Val	Leu	Arg	Glu	Asn	Thr	Ser	Pro	Lys	Ala	Asn	Lys	Glu	Ile	Leu
	755					760					765				
Asp	Glu	Ala	Tyr	Val	Met	Ala	Gly	Val	Gly	Ser	Pro	Tyr	Val	Ser	Arg
	770					775				780					
Leu	Leu	Gly	Ile	Cys	Leu	Thr	Ser	Thr	Val	Gln	Leu	Val	Thr	Gln	Leu
785				790						795					800
Met	Pro	Tyr	Gly	Cys	Leu	Leu	Asp	His	Val	Arg	Glu	Asn	Arg	Gly	Arg
			805						810					815	
Leu	Gly	Ser	Gln	Asp	Leu	Leu	Asn	Trp	Cys	Met	Gln	Ile	Ala	Lys	Gly
			820				825					830			
Met	Ser	Tyr	Leu	Glu	Asp	Val	Arg	Leu	Val	His	Arg	Asp	Leu	Ala	Ala

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835	840	845
Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe		
850	855	860
Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala Asp		
865	870	875
Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu Arg		880
	885	890
Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val		895
	900	905
Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala		910
	915	920
Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro		925
	930	935
Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met		940
945	950	955
Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu Phe		960
	965	970
Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu		975
	980	985
Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu		990
	995	1000
Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr Leu		1005
	1010	1015
Val Pro Gln Gln Gly Phe Phe Cys Pro Asp Pro Ala Pro Gly Ala Gly		1020
1025	1030	1035
Gly Met Val His His Arg His Arg Ser Ser Thr Arg Ser Gly Gly		1040
	1045	1050
Gly Asp Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu Glu Ala Pro Arg		1055
	1060	1065
Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser Asp Val Phe Asp Gly		1070
	1075	1080
Asp Leu Gly Met Gly Ala Ala Lys Gly Leu Gln Ser Leu Pro Thr His		1085
	1090	1095
Asp Pro Ser Pro Leu Gln Arg Tyr Ser Glu Asp Pro Thr Val Pro Leu		1100
1105	1110	1115
Pro Ser Glu Thr Asp Gly Tyr Val Ala Pro Leu Thr Cys Ser Pro Gln		1120
	1125	1130
Pro Glu Tyr Val Asn Gln Pro Asp Val Arg Pro Gln Pro Pro Ser Pro		1135
	1140	1145
Arg Glu Gly Pro Leu Pro Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu		1150
	1155	1160
Arg Pro Lys Thr Leu Ser Pro Gly Lys Asn Gly Val Val Lys Asp Val		1165
	1170	1175
Phe Ala Phe Gly Gly Ala Val Glu Asn Pro Glu Tyr Leu Thr Pro Gln		1180
1185	1190	1195
Gly Gly Ala Ala Pro Gln Pro His Pro Pro Pro Ala Phe Ser Pro Ala		1200
	1205	1210
Phe Asp Asn Leu Tyr Tyr Trp Asp Gln Asp Pro Pro Glu Arg Gly Ala		1215
	1220	1225
Pro Pro Ser Thr Phe Lys Gly Thr Pro Thr Ala Glu Asn Pro Glu Tyr		1230
	1235	1240
Leu Gly Leu Asp Val Pro Val		1245
	1250	1255

&lt;210&gt; 267

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&lt;211&gt; 1342

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. NP001973

&lt;309&gt; 2004-12-20

&lt;400&gt; 267

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Met Arg Ala Asn Asp Ala Leu Gln Val Leu Gly Leu Leu Phe Ser Leu
 1           5           10           15
Ala Arg Gly Ser Glu Val Gly Asn Ser Gln Ala Val Cys Pro Gly Thr
      20           25           30
Leu Asn Gly Leu Ser Val Thr Gly Asp Ala Glu Asn Gln Tyr Gln Thr
      35           40           45
Leu Tyr Lys Leu Tyr Glu Arg Cys Glu Val Val Met Gly Asn Leu Glu
      50           55           60
Ile Val Leu Thr Gly His Asn Ala Asp Leu Ser Phe Leu Gln Trp Ile
      65           70           75           80
Arg Glu Val Thr Gly Tyr Val Leu Val Ala Met Asn Glu Phe Ser Thr
      85           90           95
Leu Pro Leu Pro Asn Leu Arg Val Val Arg Gly Thr Gln Val Tyr Asp
      100          105          110
Gly Lys Phe Ala Ile Phe Val Met Leu Asn Tyr Asn Thr Asn Ser Ser
      115          120          125
His Ala Leu Arg Gln Leu Arg Leu Thr Gln Leu Thr Glu Ile Leu Ser
      130          135          140
Gly Gly Val Tyr Ile Glu Lys Asn Asp Lys Leu Cys His Met Asp Thr
      145          150          155          160
Ile Asp Trp Arg Asp Ile Val Arg Asp Arg Asp Ala Glu Ile Val Val
      165          170          175
Lys Asp Asn Gly Arg Ser Cys Pro Pro Cys His Glu Val Cys Lys Gly
      180          185          190
Arg Cys Trp Gly Pro Gly Ser Glu Asp Cys Gln Thr Leu Thr Lys Thr
      195          200          205
Ile Cys Ala Pro Gln Cys Asn Gly His Cys Phe Gly Pro Asn Pro Asn
      210          215          220
Gln Cys Cys His Asp Glu Cys Ala Gly Gly Cys Ser Gly Pro Gln Asp
      225          230          235          240
Thr Asp Cys Phe Ala Cys Arg His Phe Asn Asp Ser Gly Ala Cys Val
      245          250          255
Pro Arg Cys Pro Gln Pro Leu Val Tyr Asn Lys Leu Thr Phe Gln Leu
      260          265          270
Glu Pro Asn Pro His Thr Lys Tyr Gln Tyr Gly Gly Val Cys Val Ala
      275          280          285
Ser Cys Pro His Asn Phe Val Val Asp Gln Thr Ser Cys Val Arg Ala
      290          295          300
Cys Pro Pro Asp Lys Met Glu Val Asp Lys Asn Gly Leu Lys Met Cys
      305          310          315          320
Glu Pro Cys Gly Gly Leu Cys Pro Lys Ala Cys Glu Gly Thr Gly Ser
      325          330          335
Gly Ser Arg Phe Gln Thr Val Asp Ser Ser Asn Ile Asp Gly Phe Val
      340          345          350
Asn Cys Thr Lys Ile Leu Gly Asn Leu Asp Phe Leu Ile Thr Gly Leu
      355          360          365
Asn Gly Asp Pro Trp His Lys Ile Pro Ala Leu Asp Pro Glu Lys Leu

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370	375	380
Asn Val Phe Arg Thr	Val Arg Glu Ile Thr	Gly Tyr Leu Asn Ile Gln
385	390	395
Ser Trp Pro Pro His	Met His Asn Phe Ser	Val Phe Ser Asn Leu Thr
405	410	415
Thr Ile Gly Gly Arg	Ser Leu Tyr Asn Arg	Gly Phe Ser Leu Leu Ile
420	425	430
Met Lys Asn Leu Asn	Val Thr Ser Leu Gly	Phe Arg Ser Leu Lys Glu
435	440	445
Ile Ser Ala Gly Arg	Ile Tyr Ile Ser Ala	Asn Arg Gln Leu Cys Tyr
450	455	460
His His Ser Leu Asn	Trp Thr Lys Val Leu	Arg Gly Pro Thr Glu Glu
465	470	475
Arg Leu Asp Ile Lys	His Asn Arg Pro Arg	Arg Asp Cys Val Ala Glu
485	490	495
Gly Lys Val Cys Asp	Pro Leu Cys Ser Ser	Gly Gly Cys Trp Gly Pro
500	505	510
Gly Pro Gly Gln Cys	Leu Ser Cys Arg Asn	Tyr Ser Arg Gly Gly Val
515	520	525
Cys Val Thr His Cys	Asn Phe Leu Asn Gly	Glu Pro Arg Glu Phe Ala
530	535	540
His Glu Ala Glu Cys	Phe Ser Cys His Pro	Glu Cys Gln Pro Met Glu
545	550	555
Gly Thr Ala Thr Cys	Asn Gly Ser Gly Ser	Asp Thr Cys Ala Gln Cys
565	570	575
Ala His Phe Arg Asp	Gly Pro His Cys Val	Ser Ser Cys Pro His Gly
580	585	590
Val Leu Gly Ala Lys	Gly Pro Ile Tyr Lys	Tyr Pro Asp Val Gln Asn
595	600	605
Glu Cys Arg Pro Cys	His Glu Asn Cys Thr	Gln Gly Cys Lys Gly Pro
610	615	620
Glu Leu Gln Asp Cys	Leu Gly Gln Thr Leu	Val Leu Ile Gly Lys Thr
625	630	635
His Leu Thr Met Ala	Leu Thr Val Ile Ala	Gly Leu Val Val Ile Phe
645	650	655
Met Met Leu Gly Gly	Thr Phe Leu Tyr Trp	Arg Gly Arg Arg Ile Gln
660	665	670
Asn Lys Arg Ala Met	Arg Arg Tyr Leu Glu	Arg Gly Glu Ser Ile Glu
675	680	685
Pro Leu Asp Pro Ser	Glu Lys Ala Asn Lys	Val Leu Ala Arg Ile Phe
690	695	700
Lys Glu Thr Glu Leu	Arg Lys Leu Lys Val	Leu Gly Ser Gly Val Phe
705	710	715
Gly Thr Val His Lys	Gly Val Trp Ile Pro	Glu Gly Glu Ser Ile Lys
725	730	735
Ile Pro Val Cys Ile	Lys Val Ile Glu Asp	Lys Ser Gly Arg Gln Ser
740	745	750
Phe Gln Ala Val Thr	Asp His Met Leu Ala	Ile Gly Ser Leu Asp His
755	760	765
Ala His Ile Val Arg	Leu Leu Gly Leu Cys	Pro Gly Ser Ser Leu Gln
770	775	780
Leu Val Thr Gln Tyr	Leu Pro Leu Gly Ser	Leu Leu Asp His Val Arg
785	790	795
Gln His Arg Gly Ala	Leu Gly Pro Gln Leu	Leu Leu Asn Trp Gly Val
805	810	815
Gln Ile Ala Lys Gly	Met Tyr Tyr Leu Glu	Glu His Gly Met Val His

Arg	Asn	Leu	Ala	Ala	Arg	Asn	Val	Leu	Leu	Lys	Ser	Pro	Ser	Gln	Val
		835					840					845			
Gln	Val	Ala	Asp	Phe	Gly	Val	Ala	Asp	Leu	Leu	Pro	Pro	Asp	Asp	Lys
	850					855					860				
Gln	Leu	Leu	Tyr	Ser	Glu	Ala	Lys	Thr	Pro	Ile	Lys	Trp	Met	Ala	Leu
865					870					875					880
Glu	Ser	Ile	His	Phe	Gly	Lys	Tyr	Thr	His	Gln	Ser	Asp	Val	Trp	Ser
				885					890					895	
Tyr	Gly	Val	Thr	Val	Trp	Glu	Leu	Met	Thr	Phe	Gly	Ala	Glu	Pro	Tyr
			900					905					910		
Ala	Gly	Leu	Arg	Leu	Ala	Glu	Val	Pro	Asp	Leu	Leu	Glu	Lys	Gly	Glu
	915						920					925			
Arg	Leu	Ala	Gln	Pro	Gln	Ile	Cys	Thr	Ile	Asp	Val	Tyr	Met	Val	Met
	930					935					940				
Val	Lys	Cys	Trp	Met	Ile	Asp	Glu	Asn	Ile	Arg	Pro	Thr	Phe	Lys	Glu
945					950					955					960
Leu	Ala	Asn	Glu	Phe	Thr	Arg	Met	Ala	Arg	Asp	Pro	Pro	Arg	Tyr	Leu
				965					970					975	
Val	Ile	Lys	Arg	Glu	Ser	Gly	Pro	Gly	Ile	Ala	Pro	Gly	Pro	Glu	Pro
			980					985					990		
His	Gly	Leu	Thr	Asn	Lys	Lys	Leu	Glu	Glu	Val	Glu	Leu	Glu	Pro	Glu
	995						1000					1005			
Leu	Asp	Leu	Asp	Leu	Asp	Leu	Glu	Ala	Glu	Glu	Asp	Asn	Leu	Ala	Thr
	1010					1015					1020				
Thr	Thr	Leu	Gly	Ser	Ala	Leu	Ser	Leu	Pro	Val	Gly	Thr	Leu	Asn	Arg
1025					1030					1035					1040
Pro	Arg	Gly	Ser	Gln	Ser	Leu	Leu	Ser	Pro	Ser	Ser	Gly	Tyr	Met	Pro
				1045					1050					1055	
Met	Asn	Gln	Gly	Asn	Leu	Gly	Glu	Ser	Cys	Gln	Glu	Ser	Ala	Val	Ser
			1060						1065				1070		
Gly	Ser	Ser	Glu	Arg	Cys	Pro	Arg	Pro	Val	Ser	Leu	His	Pro	Met	Pro
			1075				1080					1085			
Arg	Gly	Cys	Leu	Ala	Ser	Glu	Ser	Ser	Glu	Gly	His	Val	Thr	Gly	Ser
	1090					1095					1100				
Glu	Ala	Glu	Leu	Gln	Glu	Lys	Val	Ser	Met	Cys	Arg	Ser	Arg	Ser	Arg
1105					1110					1115					1120
Ser	Arg	Ser	Pro	Arg	Pro	Arg	Gly	Asp	Ser	Ala	Tyr	His	Ser	Gln	Arg
				1125					1130					1135	
His	Ser	Leu	Leu	Thr	Pro	Val	Thr	Pro	Leu	Ser	Pro	Pro	Gly	Leu	Glu
			1140					1145					1150		
Glu	Glu	Asp	Val	Asn	Gly	Tyr	Val	Met	Pro	Asp	Thr	His	Leu	Lys	Gly
		1155					1160					1165			

1265					1270					1275					1280	
Ala	Cys	Pro	Ala	Ser	Glu	Gln	Gly	Tyr	Glu	Glu	Met	Arg	Ala	Phe	Gln	
				1285					1290					1295		
Gly	Pro	Gly	His	Gln	Ala	Pro	His	Val	His	Tyr	Ala	Arg	Leu	Lys	Thr	
				1300					1305					1310		
Leu	Arg	Ser	Leu	Glu	Ala	Thr	Asp	Ser	Ala	Phe	Asp	Asn	Pro	Asp	Tyr	
				1315					1320					1325		
Trp	His	Ser	Arg	Leu	Phe	Pro	Lys	Ala	Asn	Ala	Gln	Arg	Thr			
				1330					1335					1340		

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<210> 268
<211> 820
<212> PRT
<213> Homo sapiens
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<300>  
<308> GenBank No. AAA35835  
<309> 2001-12-14

<400> 268															
Met	Trp	Ser	Trp	Lys	Cys	Leu	Leu	Phe	Trp	Ala	Val	Leu	Val	Thr	Ala
1				5					10					15	
Thr	Leu	Cys	Thr	Ala	Arg	Pro	Ser	Pro	Thr	Leu	Pro	Glu	Gln	Ala	Gln
			20					25					30		
Pro	Trp	Gly	Ala	Pro	Val	Glu	Val	Glu	Ser	Phe	Leu	Val	His	Pro	Gly
		35				40					45				
Asp	Leu	Leu	Gln	Leu	Arg	Cys	Arg	Leu	Arg	Asp	Asp	Val	Gln	Ser	Ile
	50					55					60				
Asn	Trp	Leu	Arg	Asp	Gly	Val	Gln	Leu	Ala	Glu	Ser	Asn	Arg	Thr	Arg
65				70						75				80	
Ile	Thr	Gly	Glu	Glu	Val	Glu	Val	Gln	Asp	Ser	Val	Pro	Ala	Asp	Ser
			85					90						95	
Gly	Leu	Tyr	Ala	Cys	Val	Thr	Ser	Ser	Pro	Ser	Gly	Ser	Asp	Thr	Thr
			100					105					110		
Tyr	Phe	Ser	Val	Asn	Val	Ser	Asp	Ala	Leu	Pro	Ser	Ser	Glu	Asp	Asp
		115				120						125			
Asp	Asp	Asp	Asp	Asp	Ser	Ser	Ser	Glu	Glu	Lys	Glu	Thr	Asp	Asn	Thr
	130					135					140				
Lys	Pro	Asn	Pro	Val	Ala	Pro	Tyr	Trp	Thr	Ser	Pro	Glu	Lys	Met	Glu
145				150						155				160	
Lys	Lys	Leu	His	Ala	Val	Pro	Ala	Ala	Lys	Thr	Val	Lys	Phe	Lys	Cys
			165					170						175	
Pro	Ser	Ser	Gly	Thr	Pro	Asn	Pro	Thr	Leu	Arg	Trp	Leu	Lys	Asn	Ser
			180					185					190		
Lys	Glu	Phe	Lys	Pro	Asp	His	Arg	Ile	Gly	Gly	Tyr	Lys	Val	Arg	Tyr
		195				200						205			
Ala	Thr	Trp	Ser	Ile	Ile	Met	Asp	Ser	Val	Val	Pro	Ser	Asp	Lys	Gly
	210					215					220				
Asn	Tyr	Thr	Cys	Ile	Val	Glu	Asn	Glu	Tyr	Gly	Ser	Ile	Asn	His	Thr
225				230						235				240	
Tyr	Gln	Leu	Asp	Val	Val	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile	Leu	Gln
			245						250					255	
Ala	Gly	Leu	Pro	Ala	Asn	Lys	Thr	Val	Ala	Leu	Gly	Ser	Asn	Val	Glu
		260						265					270		
Phe	Met	Cys	Lys	Val	Tyr	Ser	Asp	Pro	Gln	Pro	His	Ile	Gln	Trp	Leu

			275							280							285			
Lys	His	Ile	Glu	Val	Asn	Gly	Ser	Lys	Ile	Gly	Pro	Asp	Asn	Leu	Pro					
	290					295					300									
Tyr	Val	Gln	Ile	Leu	Lys	Thr	Ala	Gly	Val	Asn	Thr	Thr	Asp	Lys	Glu					
305					310					315				320						
Met	Glu	Val	Leu	His	Leu	Arg	Asn	Val	Ser	Phe	Glu	Asp	Ala	Gly	Glu					
				325					330					335						
Tyr	Thr	Cys	Leu	Ala	Gly	Asn	Ser	Ile	Gly	Leu	Ser	His	His	Ser	Ala					
			340					345					350							
Trp	Leu	Thr	Val	Leu	Glu	Ala	Leu	Glu	Glu	Arg	Pro	Ala	Val	Met	Thr					
	355						360					365								
Ser	Pro	Leu	Tyr	Leu	Glu	Ile	Ile	Ile	Tyr	Cys	Thr	Gly	Ala	Phe	Leu					
	370					375					380									
Ile	Ser	Cys	Met	Val	Gly	Ser	Val	Ile	Val	Tyr	Lys	Met	Lys	Ser	Gly					
385					390					395				400						
Thr	Lys	Lys	Ser	Asp	Phe	His	Ser	Gln	Met	Ala	Val	His	Lys	Leu	Ala					
				405					410					415						
Lys	Ser	Ile	Pro	Leu	Arg	Arg	Gln	Val	Thr	Val	Ser	Ala	Asp	Ser	Ser					
			420					425					430							
Ala	Ser	Met	Asn	Ser	Gly	Val	Leu	Leu	Val	Arg	Pro	Ser	Arg	Leu	Ser					
	435					440					445									
Ser	Ser	Gly	Thr	Pro	Met	Leu	Ala	Gly	Val	Ser	Glu	Tyr	Glu	Leu	Pro					
	450					455					460									
Glu	Asp	Pro	Arg	Trp	Glu	Leu	Pro	Arg	Asp	Arg	Leu	Val	Leu	Gly	Lys					
465					470				475					480						
Pro	Leu	Gly	Glu	Gly	Cys	Phe	Gly	Gln	Val	Val	Leu	Ala	Glu	Ala	Ile					
				485					490					495						
Gly	Leu	Asp	Lys	Asp	Lys	Pro	Asn	Arg	Val	Thr	Lys	Val	Ala	Val	Lys					
			500					505					510							
Met	Leu	Lys	Ser	Asp	Ala	Thr	Glu	Lys	Asp	Leu	Ser	Asp	Leu	Ile	Ser					
	515						520					525								
Glu	Met	Glu	Met	Met	Lys	Met	Ile	Gly	Lys	His	Lys	Asn	Ile	Ile	Asn					
	530					535					540									
Leu	Leu	Gly	Ala	Cys	Thr	Gln	Asp	Gly	Pro	Leu	Tyr	Val	Ile	Val	Glu					
545					550				555					560						
Tyr	Ala	Ser	Lys	Gly	Asn	Leu	Arg	Glu	Tyr	Leu	Gln	Ala	Arg	Arg	Pro					
				565					570					575						
Pro	Gly	Leu	Glu	Tyr	Cys	Tyr	Asn	Pro	Ser	His	Asn	Pro	Glu	Glu	Gln					
			580					585					590							
Leu	Ser	Ser	Lys	Asp	Leu	Val	Ser	Cys	Ala	Tyr	Gln	Val	Ala	Arg	Gly					
	595						600					605					</			



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              725              730              735
Ala Val Pro Ser Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu
              740              745              750
Asp Arg Ile Val Ala Leu Thr Ser Asn Gln Glu Tyr Leu Asp Leu Ser
              755              760              765
Met Pro Leu Asp Gln Tyr Ser Pro Ser Phe Pro Asp Thr Arg Ser Ser
              770              775              780
Thr Cys Ser Ser Gly Glu Asp Ser Val Phe Ser His Glu Pro Leu Pro
785              790              795              800
Glu Glu Pro Cys Leu Pro Arg His Pro Ala Gln Leu Ala Asn Gly Gly
              805              810              815
Leu Lys Arg Arg
              820

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<210> 269  
 <211> 821  
 <212> PRT  
 <213> Homo sapiens

<300>  
 <308> GenBank No. NP000132  
 <309> 2004-12-20

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<400> 269
Met Val Ser Trp Gly Arg Phe Ile Cys Leu Val Val Val Thr Met Ala
1              5              10              15
Thr Leu Ser Leu Ala Arg Pro Ser Phe Ser Leu Val Glu Asp Thr Thr
              20              25              30
Leu Glu Pro Glu Glu Pro Pro Thr Lys Tyr Gln Ile Ser Gln Pro Glu
              35              40              45
Val Tyr Val Ala Ala Pro Gly Glu Ser Leu Glu Val Arg Cys Leu Leu
              50              55              60
Lys Asp Ala Ala Val Ile Ser Trp Thr Lys Asp Gly Val His Leu Gly
65              70              75              80
Pro Asn Asn Arg Thr Val Leu Ile Gly Glu Tyr Leu Gln Ile Lys Gly
              85              90              95
Ala Thr Pro Arg Asp Ser Gly Leu Tyr Ala Cys Thr Ala Ser Arg Thr
              100              105              110
Val Asp Ser Glu Thr Trp Tyr Phe Met Val Asn Val Thr Asp Ala Ile
              115              120              125
Ser Ser Gly Asp Asp Glu Asp Asp Thr Asp Gly Ala Glu Asp Phe Val
              130              135              140
Ser Glu Asn Ser Asn Asn Lys Arg Ala Pro Tyr Trp Thr Asn Thr Glu
145              150              155              160
Lys Met Glu Lys Arg Leu His Ala Val Pro Ala Ala Asn Thr Val Lys
              165              170              175
Phe Arg Cys Pro Ala Gly Gly Asn Pro Met Pro Thr Met Arg Trp Leu
              180              185              190
Lys Asn Gly Lys Glu Phe Lys Gln Glu His Arg Ile Gly Gly Tyr Lys
              195              200              205
Val Arg Asn Gln His Trp Ser Leu Ile Met Glu Ser Val Val Pro Ser
210              215              220
Asp Lys Gly Asn Tyr Thr Cys Val Val Glu Asn Glu Tyr Gly Ser Ile
225              230              235              240
Asn His Thr Tyr His Leu Asp Val Val Glu Arg Ser Pro His Arg Pro

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				245					250					255	
Ile	Leu	Gln	Ala	Gly	Leu	Pro	Ala	Asn	Ala	Ser	Thr	Val	Val	Gly	Gly
			260					265					270		
Asp	Val	Glu	Phe	Val	Cys	Lys	Val	Tyr	Ser	Asp	Ala	Gln	Pro	His	Ile
		275					280					285			
Gln	Trp	Ile	Lys	His	Val	Glu	Lys	Asn	Gly	Ser	Lys	Tyr	Gly	Pro	Asp
	290					295					300				
Gly	Leu	Pro	Tyr	Leu	Lys	Val	Leu	Lys	Ala	Ala	Gly	Val	Asn	Thr	Thr
305				310					315					320	
Asp	Lys	Glu	Ile	Glu	Val	Leu	Tyr	Ile	Arg	Asn	Val	Thr	Phe	Glu	Asp
			325					330					335		
Ala	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly	Asn	Ser	Ile	Gly	Ile	Ser	Phe
		340					345					350			
His	Ser	Ala	Trp	Leu	Thr	Val	Leu	Pro	Ala	Pro	Gly	Arg	Glu	Lys	Glu
	355					360					365				
Ile	Thr	Ala	Ser	Pro	Asp	Tyr	Leu	Glu	Ile	Ala	Ile	Tyr	Cys	Ile	Gly
370					375						380				
Val	Phe	Leu	Ile	Ala	Cys	Met	Val	Val	Thr	Val	Ile	Leu	Cys	Arg	Met
385				390					395					400	
Lys	Asn	Thr	Thr	Lys	Lys	Pro	Asp	Phe	Ser	Ser	Gln	Pro	Ala	Val	His
			405					410					415		
Lys	Leu	Thr	Lys	Arg	Ile	Pro	Leu	Arg	Arg	Gln	Val	Thr	Val	Ser	Ala
		420					425					430			
Glu	Ser	Ser	Ser	Ser	Met	Asn	Ser	Asn	Thr	Pro	Leu	Val	Arg	Ile	Thr
	435					440					445				
Thr	Arg	Leu	Ser	Ser	Thr	Ala	Asp	Thr	Pro	Met	Leu	Ala	Gly	Val	Ser
450					455						460				
Glu	Tyr	Glu	Leu	Pro	Glu	Asp	Pro	Lys	Trp	Glu	Phe	Pro	Arg	Asp	Lys
465				470					475					480	
Leu	Thr	Leu	Gly	Lys	Pro	Leu	Gly	Glu	Gly	Cys	Phe	Gly	Gln	Val	Val
			485					490					495		
Met	Ala	Glu	Ala	Val	Gly	Ile	Asp	Lys	Asp	Lys	Pro	Lys	Glu	Ala	Val
		500					505					510			
Thr	Val	Ala	Val	Lys	Met	Leu	Lys	Asp	Asp	Ala	Thr	Glu	Lys	Asp	Leu
	515						520					525			
Ser	Asp	Leu	Val	Ser	Glu	Met	Glu	Met	Met	Lys	Met	Ile	Gly	Lys	His
	530				535						540				
Lys	Asn	Ile	Ile	Asn	Leu	Leu	Gly	Ala	Cys	Thr	Gln	Asp	Gly	Pro	Leu
545				550					555					560	
Tyr	Val	Ile	Val	Glu	Tyr	Ala	Ser	Lys	Gly	Asn	Leu	Arg	Glu	Tyr	Leu
		565						570					575		
Arg	Ala	Arg	Arg	Pro	Pro	Gly	Met	Glu	Tyr	Ser	Tyr	Asp	Ile	Asn	Arg
		580					585						590		
Val	Pro	Glu	Gln	Met	Thr	Phe	Lys	Asp	Leu	Val	Ser	Cys	Thr	Tyr	
	595					600					605				
Gln	Leu	Ala	Arg	Gly	Met	Glu	Tyr	Leu	Ala	Ser	Gln	Lys	Cys	Ile	His
	610				615						620				
Arg	Asp	Leu	Ala	Ala	Arg	Asn	Val	Leu	Val	Thr	Glu	Asn	Asn	Val	Met
625				630					635					640	
Lys	Ile	Ala	Asp	Phe	Gly	Leu	Ala	Arg	Asp	Ile	Asn	Asn	Ile	Asp	Tyr
		645						650					655		
Tyr	Lys	Lys	Thr	Thr	Asn	Gly	Arg	Leu	Pro	Val	Lys	Trp	Met	Ala	Pro
	660						665						670		
Glu	Ala	Leu	Phe	Asp	Arg	Val	Tyr	Thr	His	Gln	Ser	Asp	Val	Trp	Ser
	675				680							685			
Phe	Gly	Val	Leu	Met	Trp	Glu	Ile	Phe	Thr	Leu	Gly	Gly	Ser	Pro	Tyr

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      690              695              700
Pro Gly Ile Pro Val Glu Glu Leu Phe Lys Leu Leu Lys Glu Gly His
705              710              715
Arg Met Asp Lys Pro Ala Asn Cys Thr Asn Glu Leu Tyr Met Met Met
              725              730              735
Arg Asp Cys Trp His Ala Val Pro Ser Gln Arg Pro Thr Phe Lys Gln
              740              745              750
Leu Val Glu Asp Leu Asp Arg Ile Leu Thr Leu Thr Thr Asn Glu Glu
              755              760              765
Tyr Leu Asp Leu Ser Gln Pro Leu Glu Gln Tyr Ser Pro Ser Tyr Pro
              770              775              780
Asp Thr Arg Ser Ser Cys Ser Ser Gly Asp Asp Ser Val Phe Ser Pro
785              790              795
Asp Pro Met Pro Tyr Glu Pro Cys Leu Pro Gln Tyr Pro His Ile Asn
              805              810              815
Gly Ser Val Lys Thr
              820

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<210> 270  
 <211> 806  
 <212> PRT  
 <213> Homo sapiens

<300>  
 <308> GenBank No. NP000133  
 <309> 2004-12-20

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Val Ala Gly Ala Ser Ser Glu Ser Leu Gly Thr Glu Gln Arg Val Val
              20              25              30
Gly Arg Ala Ala Glu Val Pro Gly Pro Glu Pro Gly Gln Gln Glu Gln
              35              40              45
Leu Val Phe Gly Ser Gly Asp Ala Val Glu Leu Ser Cys Pro Pro Pro
50              55              60
Gly Gly Gly Pro Met Gly Pro Thr Val Trp Val Lys Asp Gly Thr Gly
65              70              75              80
Leu Val Pro Ser Glu Arg Val Leu Val Gly Pro Gln Arg Leu Gln Val
              85              90              95
Leu Asn Ala Ser His Glu Asp Ser Gly Ala Tyr Ser Cys Arg Gln Arg
100              105              110
Leu Thr Gln Arg Val Leu Cys His Phe Ser Val Arg Val Thr Asp Ala
115              120              125
Pro Ser Ser Gly Asp Asp Glu Asp Gly Glu Asp Glu Ala Glu Asp Thr
130              135              140
Gly Val Asp Thr Gly Ala Pro Tyr Trp Thr Arg Pro Glu Arg Met Asp
145              150              155              160
Lys Lys Leu Leu Ala Val Pro Ala Ala Asn Thr Val Arg Phe Arg Cys
              165              170              175
Pro Ala Ala Gly Asn Pro Thr Pro Ser Ile Ser Trp Leu Lys Asn Gly
180              185              190
Arg Glu Phe Arg Gly Glu His Arg Ile Gly Gly Ile Lys Leu Arg His
195              200              205
Gln Gln Trp Ser Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly

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210					215					220									
Asn	Tyr	Thr	Cys	Val	Val	Glu	Asn	Lys	Phe	Gly	Ser	Ile	Arg	Gln	Thr				
225					230					235					240				
Tyr	Thr	Leu	Asp	Val	Leu	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile	Leu	Gln				
				245					250					255					
Ala	Gly	Leu	Pro	Ala	Asn	Gln	Thr	Ala	Val	Leu	Gly	Ser	Asp	Val	Glu				
				260				265					270						
Phe	His	Cys	Lys	Val	Tyr	Ser	Asp	Ala	Gln	Pro	His	Ile	Gln	Trp	Leu				
		275					280					285							
Lys	His	Val	Glu	Val	Asn	Gly	Ser	Lys	Val	Gly	Pro	Asp	Gly	Thr	Pro				
	290					295					300								
Tyr	Val	Thr	Val	Leu	Lys	Thr	Ala	Gly	Ala	Asn	Thr	Thr	Asp	Lys	Glu				
305					310					315					320				
Leu	Glu	Val	Leu	Ser	Leu	His	Asn	Val	Thr	Phe	Glu	Asp	Ala	Gly	Glu				
				325						330				335					
Tyr	Thr	Cys	Leu	Ala	Gly	Asn	Ser	Ile	Gly	Phe	Ser	His	His	Ser	Ala				
			340				345						350						
Trp	Leu	Val	Val	Leu	Pro	Ala	Glu	Glu	Glu	Leu	Val	Glu	Ala	Asp	Glu				
		355					360					365							
Ala	Gly	Ser	Val	Tyr	Ala	Gly	Ile	Leu	Ser	Tyr	Gly	Val	Gly	Phe	Phe				
	370					375					380								
Leu	Phe	Ile	Leu	Val	Val	Ala	Ala	Val	Thr	Leu	Cys	Arg	Leu	Arg	Ser				
385					390					395					400				
Pro	Pro	Lys	Lys	Gly	Leu	Gly	Ser	Pro	Thr	Val	His	Lys	Ile	Ser	Arg				
				405					410					415					
Phe	Pro	Leu	Lys	Arg	Gln	Val	Ser	Leu	Glu	Ser	Asn	Ala	Ser	Met	Ser				
			420				425						430						
Ser	Asn	Thr	Pro	Leu	Val	Arg	Ile	Ala	Arg	Leu	Ser	Ser	Gly	Glu	Gly				
		435					440					445							
Pro	Thr	Leu	Ala	Asn	Val	Ser	Glu	Leu	Glu	Leu	Pro	Ala	Asp	Pro	Lys				
	450					455					460								
Trp	Glu	Leu	Ser	Arg	Ala	Arg	Leu	Thr	Leu	Gly	Lys	Pro	Leu	Gly	Glu				
465					470					475					480				
Gly	Cys	Phe	Gly	Gln	Val	Val	Met	Ala	Glu	Ala	Ile	Gly	Ile	Asp	Lys				
				485					490					495					
Asp	Arg	Ala	Ala	Lys	Pro	Val	Thr	Val	Ala	Val	Lys	Met	Leu	Lys	Asp				
			500					505					510						
Asp	Ala	Thr	Asp	Lys	Asp	Leu	Ser	Asp	Leu	Val	Ser	Glu	Met	Glu	Met				
		515					520					525							
Met	Lys	Met	Ile	Gly	Lys	His	Lys	Asn	Ile	Ile	Asn	Leu	Leu	Gly	Ala				
	530					535					540								
Cys	Thr	Gln	Gly	Gly	Pro	Leu	Tyr	Val	Leu	Val	Glu	Tyr	Ala	Ala	Lys				
545					550					555									

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        660                665                670
His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe
        675                680                685
Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe
        690                695                700
Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn Cys Thr
705                710                715                720
His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala Pro Ser
        725                730                735
Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Val Leu
        740                745                750
Thr Val Thr Ser Thr Asp Glu Tyr Leu Asp Leu Ser Ala Pro Phe Glu
        755                760                765
Gln Tyr Ser Pro Gly Gly Gln Asp Thr Pro Ser Ser Ser Ser Ser Gly
770                775                780
Asp Asp Ser Val Phe Ala His Asp Leu Leu Pro Pro Ala Pro Pro Ser
785                790                795                800
Ser Gly Gly Ser Arg Thr
        805

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&lt;210&gt; 271

&lt;211&gt; 802

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. NP002002

&lt;309&gt; 2004-10-28

&lt;400&gt; 271

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Met Arg Leu Leu Leu Ala Leu Leu Gly Val Leu Leu Ser Val Pro Gly
 1                5                10                15
Pro Pro Val Leu Ser Leu Glu Ala Ser Glu Glu Val Glu Leu Glu Pro
        20                25                30
Cys Leu Ala Pro Ser Leu Glu Gln Gln Glu Leu Thr Val Ala
        35                40                45
Leu Gly Gln Pro Val Arg Leu Cys Cys Gly Arg Ala Glu Arg Gly Gly
50                55                60
His Trp Tyr Lys Glu Gly Ser Arg Leu Ala Pro Ala Gly Arg Val Arg
65                70                75                80
Gly Trp Arg Gly Arg Leu Glu Ile Ala Ser Phe Leu Pro Glu Asp Ala
        85                90                95
Gly Arg Tyr Leu Cys Leu Ala Arg Gly Ser Met Ile Val Leu Gln Asn
        100                105                110
Leu Thr Leu Ile Thr Gly Asp Ser Leu Thr Ser Ser Asn Asp Asp Glu
        115                120                125
Asp Pro Lys Ser His Arg Asp Pro Ser Asn Arg His Ser Tyr Pro Gln
130                135                140
Gln Ala Pro Tyr Trp Thr His Pro Gln Arg Met Glu Lys Lys Leu His
145                150                155                160
Ala Val Pro Ala Gly Asn Thr Val Lys Phe Arg Cys Pro Ala Ala Gly
        165                170                175
Asn Pro Thr Pro Thr Ile Arg Trp Leu Lys Asp Gly Gln Ala Phe His
180                185                190
Gly Glu Asn Arg Ile Gly Gly Ile Arg Leu Arg His Gln His Trp Ser

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		195					200					205					
Leu	Val	Met	Glu	Ser	Val	Val	Pro	Ser	Asp	Arg	Gly	Thr	Tyr	Thr	Cys		
	210					215					220						
Leu	Val	Glu	Asn	Ala	Val	Gly	Ser	Ile	Arg	Tyr	Asn	Tyr	Leu	Leu	Asp		
225					230					235					240		
Val	Leu	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile	Leu	Gln	Ala	Gly	Leu	Pro		
				245				250					255				
Ala	Asn	Thr	Thr	Ala	Val	Val	Gly	Ser	Asp	Val	Glu	Leu	Leu	Cys	Lys		
			260				265					270					
Val	Tyr	Ser	Asp	Ala	Gln	Pro	His	Ile	Gln	Trp	Leu	Lys	His	Ile	Val		
	275					280					285						
Ile	Asn	Gly	Ser	Ser	Phe	Gly	Ala	Asp	Gly	Phe	Pro	Tyr	Val	Gln	Val		
	290					295				300							
Leu	Lys	Thr	Ala	Asp	Ile	Asn	Ser	Ser	Glu	Val	Glu	Val	Leu	Tyr	Leu		
305					310					315					320		
Arg	Asn	Val	Ser	Ala	Glu	Asp	Ala	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly		
				325				330					335				
Asn	Ser	Ile	Gly	Leu	Ser	Tyr	Gln	Ser	Ala	Trp	Leu	Thr	Val	Leu	Pro		
			340				345					350					
Glu	Glu	Asp	Pro	Thr	Trp	Thr	Ala	Ala	Ala	Pro	Glu	Ala	Arg	Tyr	Thr		
		355				360				365							
Asp	Ile	Ile	Leu	Tyr	Ala	Ser	Gly	Ser	Leu	Ala	Leu	Ala	Val	Leu	Leu		
	370					375				380							
Leu	Leu	Ala	Gly	Leu	Tyr	Arg	Gly	Gln	Ala	Leu	His	Gly	Arg	His	Pro		
385					390				395						400		
Arg	Pro	Pro	Ala	Thr	Val	Gln	Lys	Leu	Ser	Arg	Phe	Pro	Leu	Ala	Arg		
				405				410					415				
Gln	Phe	Ser	Leu	Glu	Ser	Gly	Ser	Ser	Gly	Lys	Ser	Ser	Ser	Ser	Leu		
			420				425					430					
Val	Arg	Gly	Val	Arg	Leu	Ser	Ser	Ser	Gly	Pro	Ala	Leu	Leu	Ala	Gly		
		435				440				445							
Leu	Val	Ser	Leu	Asp	Leu	Pro	Leu	Asp	Pro	Leu	Trp	Glu	Phe	Pro	Arg		
	450					455				460							
Asp	Arg	Leu	Val	Leu	Gly	Lys	Pro	Leu	Gly	Glu	Gly	Cys	Phe	Gly	Gln		
465					470				475						480		
Val	Val	Arg	Ala	Glu	Ala	Phe	Gly	Met	Asp	Pro	Ala	Arg	Pro	Asp	Gln		
				485				490					495				
Ala	Ser	Thr	Val	Ala	Val	Lys	Met	Leu	Lys	Asp	Asn	Ala	Ser	Asp	Lys		
			500				505				510						
Asp	Leu	Ala	Asp	Leu	Val	Ser	Glu	Met	Glu	Val	Met	Lys	Leu	Ile	Gly		
		515					520				525						
Arg	His	Lys	Asn	Ile	Ile	Asn	Leu	Leu	Gly	Val	Cys	Thr	Gln	Glu	Gly		
	530					535					540						
Pro	Leu	Tyr	Val	Ile	Val	Glu	Cys	Ala	Ala	Lys	Gly	Asn	Leu	Arg	Glu		
545					550												

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				645					650					655					
Ala	Pro	Glu	Ala	Leu	Phe	Asp	Arg	Val	Tyr	Thr	His	Gln	Ser	Asp	Val				
			660					665					670						
Trp	Ser	Phe	Gly	Ile	Leu	Leu	Trp	Glu	Ile	Phe	Thr	Leu	Gly	Gly	Ser				
		675					680					685							
Pro	Tyr	Pro	Gly	Ile	Pro	Val	Glu	Glu	Leu	Phe	Ser	Leu	Leu	Arg	Glu				
		690				695					700								
Gly	His	Arg	Met	Asp	Arg	Pro	Pro	His	Cys	Pro	Pro	Glu	Leu	Tyr	Gly				
705					710					715					720				
Leu	Met	Arg	Glu	Cys	Trp	His	Ala	Ala	Pro	Ser	Gln	Arg	Pro	Thr	Phe				
				725					730						735				
Lys	Gln	Leu	Val	Glu	Ala	Leu	Asp	Lys	Val	Leu	Leu	Ala	Val	Ser	Glu				
		740						745					750						
Glu	Tyr	Leu	Asp	Leu	Arg	Leu	Thr	Phe	Gly	Pro	Tyr	Ser	Pro	Ser	Gly				
		755					760					765							
Gly	Asp	Ala	Ser	Ser	Thr	Cys	Ser	Ser	Ser	Asp	Ser	Val	Phe	Ser	His				
770						775					780								
Asp	Pro	Leu	Pro	Leu	Gly	Ser	Ser	Ser	Phe	Pro	Phe	Gly	Ser	Gly	Val				
785					790					795					800				
Gln	Thr																		

&lt;210&gt; 272

&lt;211&gt; 993

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. NP004110

&lt;309&gt; 2005-01-22

&lt;400&gt; 272

Met	Pro	Ala	Leu	Ala	Arg	Asp	Ala	Gly	Thr	Val	Pro	Leu	Leu	Val	Val				
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Phe	Ser	Ala	Met	Ile	Phe	Gly	Thr	Ile	Thr	Asn	Gln	Asp	Leu	Pro	Val				
		20					25						30						
Ile	Lys	Cys	Val	Leu	Ile	Asn	His	Lys	Asn	Asn	Asp	Ser	Ser	Val	Gly				
		35				40					45								
Lys	Ser	Ser	Ser	Tyr	Pro	Met	Val	Ser	Glu	Ser	Pro	Glu	Asp	Leu	Gly				
		50				55					60								
Cys	Ala	Leu	Arg	Pro	Gln	Ser	Ser	Gly	Thr	Val	Tyr	Glu	Ala	Ala	Ala				
65				70						75				80					
Val	Glu	Val	Asp	Val	Ser	Ala	Ser	Ile	Thr	Leu	Gln	Val	Leu	Val	Asp				
			85					90						95					
Ala	Pro	Gly	Asn	Ile	Ser	Cys	Leu	Trp	Val	Phe	Lys	His	Ser	Ser	Leu				
			100					105					110						
Asn	Cys	Gln	Pro	His	Phe	Asp	Leu	Gln	Asn	Arg	Gly	Val	Val	Ser	Met				
		115				120					125								
Val	Ile	Leu	Lys	Met	Thr	Glu	Thr	Gln	Ala	Gly	Glu	Tyr	Leu	Leu	Phe				
		130				135					140								
Ile	Gln	Ser	Glu	Ala	Thr	Asn	Tyr	Thr	Ile	Leu	Phe	Thr	Val	Ser	Ile				
145				150						155					160				
Arg	Asn	Thr	Leu	Leu	Tyr	Thr	Leu	Arg	Arg	Pro	Tyr	Phe	Arg	Lys	Met				
			165					170						175					
Glu	Asn	Gln	Asp	Ala	Leu	Val	Cys	Ile	Ser	Glu	Ser	Val	Pro	Glu	Pro				

				180					185					190		
Ile	Val	Glu	Trp	Val	Leu	Cys	Asp	Ser	Gln	Gly	Glu	Ser	Cys	Lys	Glu	
		195					200					205				
Glu	Ser	Pro	Ala	Val	Val	Lys	Lys	Glu	Glu	Lys	Val	Leu	His	Glu	Leu	
		210					215					220				
Phe	Gly	Thr	Asp	Ile	Arg	Cys	Cys	Ala	Arg	Asn	Glu	Leu	Gly	Arg	Glu	
225					230						235				240	
Cys	Thr	Arg	Leu	Phe	Thr	Ile	Asp	Leu	Asn	Gln	Thr	Pro	Gln	Thr	Thr	
				245					250					255		
Leu	Pro	Gln	Leu	Phe	Leu	Lys	Val	Gly	Glu	Pro	Leu	Trp	Ile	Arg	Cys	
			260					265					270			
Lys	Ala	Val	His	Val	Asn	His	Gly	Phe	Gly	Leu	Thr	Trp	Glu	Leu	Glu	
		275					280					285				
Asn	Lys	Ala	Leu	Glu	Glu	Gly	Asn	Tyr	Phe	Glu	Met	Ser	Thr	Tyr	Ser	
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Thr	Asn	Arg	Thr	Met	Ile	Arg	Ile	Leu	Phe	Ala	Phe	Val	Ser	Ser	Val	
305					310					315					320	
Ala	Arg	Asn	Asp	Thr	Gly	Tyr	Tyr	Thr	Cys	Ser	Ser	Ser	Lys	His	Pro	
				325					330					335		
Ser	Gln	Ser	Ala	Leu	Val	Thr	Ile	Val	Gly	Lys	Gly	Phe	Ile	Asn	Ala	
			340					345					350			
Thr	Asn	Ser	Ser	Glu	Asp	Tyr	Glu	Ile	Asp	Gln	Tyr	Glu	Glu	Phe	Cys	
		355					360					365				
Phe	Ser	Val	Arg	Phe	Lys	Ala	Tyr	Pro	Gln	Ile	Arg	Cys	Thr	Trp	Thr	
		370				375					380					
Phe	Ser	Arg	Lys	Ser	Phe	Pro	Cys	Glu	Gln	Lys	Gly	Leu	Asp	Asn	Gly	
385					390					395					400	
Tyr	Ser	Ile	Ser	Lys	Phe	Cys	Asn	His	Lys	His	Gln	Pro	Gly	Glu	Tyr	
				405					410					415		
Ile	Phe	His	Ala	Glu	Asn	Asp	Asp	Ala	Gln	Phe	Thr	Lys	Met	Phe	Thr	
			420					425					430			
Leu	Asn	Ile	Arg	Arg	Lys	Pro	Gln	Val	Leu	Ala	Glu	Ala	Ser	Ala	Ser	
		435					440					445				
Gln	Ala	Ser	Cys	Phe	Ser	Asp	Gly	Tyr	Pro	Leu	Pro	Ser	Trp	Thr	Trp	
		450				455					460					
Lys	Lys	Cys	Ser	Asp	Lys	Ser	Pro	Asn	Cys	Thr	Glu	Glu	Ile	Thr	Glu	
465					470					475					480	
Gly	Val	Trp	Asn	Arg	Lys	Ala	Asn	Arg	Lys	Val	Phe	Gly	Gln	Trp	Val	
				485					490					495		
Ser	Ser	Ser	Thr	Leu	Asn	Met	Ser	Glu	Ala	Ile	Lys	Gly	Phe	Leu	Val	
			500					505					510			
Lys	Cys	Cys	Ala	Tyr	Asn	Ser	Leu	Gly	Thr	Ser	Cys	Glu	Thr	Ile	Leu	
		515					520			</						



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625					630					635				640
Val	Ala	Val	Lys	Met	Leu	Lys	Glu	Lys	Ala	Asp	Ser	Ser	Glu	Arg
				645					650				655	
Ala	Leu	Met	Ser	Glu	Leu	Lys	Met	Met	Thr	Gln	Leu	Gly	Ser	His
			660					665					670	
Asn	Ile	Val	Asn	Leu	Leu	Gly	Ala	Cys	Thr	Leu	Ser	Gly	Pro	Ile
		675					680					685		
Leu	Ile	Phe	Glu	Tyr	Cys	Cys	Tyr	Gly	Asp	Leu	Leu	Asn	Tyr	Leu
	690					695					700			
Ser	Lys	Arg	Glu	Lys	Phe	His	Arg	Thr	Trp	Thr	Glu	Ile	Phe	Lys
705				710					715				720	
His	Asn	Phe	Ser	Phe	Tyr	Pro	Thr	Phe	Gln	Ser	His	Pro	Asn	Ser
			725					730					735	
Met	Pro	Gly	Ser	Arg	Glu	Val	Gln	Ile	His	Pro	Asp	Ser	Asp	Gln
		740					745					750		
Ser	Gly	Leu	His	Gly	Asn	Ser	Phe	His	Ser	Glu	Asp	Glu	Ile	Glu
	755						760					765		
Glu	Asn	Gln	Lys	Arg	Leu	Glu	Glu	Glu	Asp	Leu	Asn	Val	Leu	Thr
	770					775			780					
Phe	Glu	Asp	Leu	Leu	Cys	Phe	Ala	Tyr	Gln	Val	Ala	Lys	Gly	Met
785					790				795					800
Phe	Leu	Glu	Phe	Lys	Ser	Cys	Val	His	Arg	Asp	Leu	Ala	Ala	Arg
			805					810					815	
Val	Leu	Val	Thr	His	Gly	Lys	Val	Val	Lys	Ile	Cys	Asp	Phe	Gly
		820					825						830	
Ala	Arg	Asp	Ile	Met	Ser	Asp	Ser	Asn	Tyr	Val	Val	Arg	Gly	Asn
	835						840					845		
Arg	Leu	Pro	Val	Lys	Trp	Met	Ala	Pro	Glu	Ser	Leu	Phe	Glu	Gly
	850					855					860			
Tyr	Thr	Ile	Lys	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Ile	Leu	Leu	Trp
865					870				875					880
Ile	Phe	Ser	Leu	Gly	Val	Asn	Pro	Tyr	Pro	Gly	Ile	Pro	Val	Asp
			885						890					895
Asn	Phe	Tyr	Lys	Leu	Ile	Gln	Asn	Gly	Phe	Lys	Met	Asp	Gln	Pro
		900						905					910	
Tyr	Ala	Thr	Glu	Glu	Ile	Tyr	Ile	Ile	Met	Gln	Ser	Cys	Trp	Ala
	915						920					925		
Asp	Ser	Arg	Lys	Arg	Pro	Ser	Phe	Pro	Asn	Leu	Thr	Ser	Phe	Leu
	930					935					940			
Cys	Gln	Leu	Ala	Asp	Ala	Glu	Glu	Ala	Met	Tyr	Gln	Asn	Val	Asp
945					950				955					960
Arg	Val	Ser	Glu	Cys	Pro	His	Thr	Tyr	Gln	Asn	Arg	Arg	Pro	Phe
			965						970					975
Arg	Glu	Met	Asp	Leu	Gly	Leu	Leu	Ser	Pro	Gln	Ala	Gln	Val	Glu
			980					985					990	
Ser														

&lt;210&gt; 273

&lt;211&gt; 1363

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. NP000213

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&lt;309&gt; 2004-12-20

&lt;400&gt; 273

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Met Gln Arg Gly Ala Ala Leu Cys Leu Arg Leu Trp Leu Cys Leu Gly
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Leu Leu Asp Gly Leu Val Ser Asp Tyr Ser Met Thr Pro Pro Thr Leu
          20          25          30
Asn Ile Thr Glu Glu Ser His Val Ile Asp Thr Gly Asp Ser Leu Ser
          35          40          45
Ile Ser Cys Arg Gly Gln His Pro Leu Glu Trp Ala Trp Pro Gly Ala
          50          55          60
Gln Glu Ala Pro Ala Thr Gly Asp Lys Asp Ser Glu Asp Thr Gly Val
65          70          75          80
Val Arg Asp Cys Glu Gly Thr Asp Ala Arg Pro Tyr Cys Lys Val Leu
          85          90          95
Leu Leu His Glu Val His Ala Asn Asp Thr Gly Ser Tyr Val Cys Tyr
          100          105          110
Tyr Lys Tyr Ile Lys Ala Arg Ile Glu Gly Thr Thr Ala Ala Ser Ser
          115          120          125
Tyr Val Phe Val Arg Asp Phe Glu Gln Pro Phe Ile Asn Lys Pro Asp
130          135          140
Thr Leu Leu Val Asn Arg Lys Asp Ala Met Trp Val Pro Cys Leu Val
145          150          155          160
Ser Ile Pro Gly Leu Asn Val Thr Leu Arg Ser Gln Ser Ser Val Leu
          165          170          175
Trp Pro Asp Gly Gln Glu Val Val Trp Asp Asp Arg Arg Gly Met Leu
          180          185          190
Val Ser Thr Pro Leu Leu His Asp Ala Leu Tyr Leu Gln Cys Glu Thr
          195          200          205
Thr Trp Gly Asp Gln Asp Phe Leu Ser Asn Pro Phe Leu Val His Ile
210          215          220
Thr Gly Asn Glu Leu Tyr Asp Ile Gln Leu Leu Pro Arg Lys Ser Leu
225          230          235          240
Glu Leu Leu Val Gly Glu Lys Leu Val Leu Asn Cys Thr Val Trp Ala
          245          250          255
Glu Phe Asn Ser Gly Val Thr Phe Asp Trp Asp Tyr Pro Gly Lys Gln
          260          265          270
Ala Glu Arg Gly Lys Trp Val Pro Glu Arg Arg Ser Gln Gln Thr His
          275          280          285
Thr Glu Leu Ser Ser Ile Leu Thr Ile His Asn Val Ser Gln His Asp
290          295          300
Leu Gly Ser Tyr Val Cys Lys Ala Asn Asn Gly Ile Gln Arg Phe Arg
305          310          315          320
Glu Ser Thr Glu Val Ile Val His Glu Asn Pro Phe Ile Ser Val Glu
          325          330          335
Trp Leu Lys Gly Pro Ile Leu Glu Ala Thr Ala Gly Asp Glu Leu Val
          340          345          350
Lys Leu Pro Val Lys Leu Ala Ala Tyr Pro Pro Pro Glu Phe Gln Trp
          355          360          365
Tyr Lys Asp Gly Lys Ala Leu Ser Gly Arg His Ser Pro His Ala Leu
          370          375          380
Val Leu Lys Glu Val Thr Glu Ala Ser Thr Gly Thr Tyr Thr Leu Ala
385          390          395          400
Leu Trp Asn Ser Ala Ala Gly Leu Arg Arg Asn Ile Ser Leu Glu Leu
          405          410          415
Val Val Asn Val Pro Pro Gln Ile His Glu Lys Glu Ala Ser Ser Pro

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				420						425						430					
Ser	Ile	Tyr	Ser	Arg	His	Ser	Arg	Gln	Ala	Leu	Thr	Cys	Thr	Ala	Tyr						
				435						440						445					
Gly	Val	Pro	Leu	Pro	Leu	Ser	Ile	Gln	Trp	His	Trp	Arg	Pro	Trp	Thr						
				450						455						460					
Pro	Cys	Lys	Met	Phe	Ala	Gln	Arg	Ser	Leu	Arg	Arg	Arg	Gln	Gln	Gln						
465				470						475						480					
Asp	Leu	Met	Pro	Gln	Cys	Arg	Asp	Trp	Arg	Ala	Val	Thr	Thr	Gln	Asp						
				485						490						495					
Ala	Val	Asn	Pro	Ile	Glu	Ser	Leu	Asp	Thr	Trp	Thr	Glu	Phe	Val	Glu						
				500						505						510					
Gly	Lys	Asn	Lys	Thr	Val	Ser	Lys	Leu	Val	Ile	Gln	Asn	Ala	Asn	Val						
				515						520						525					
Ser	Ala	Met	Tyr	Lys	Cys	Val	Val	Ser	Asn	Lys	Val	Gly	Gln	Asp	Glu						
				530						535						540					
Arg	Leu	Ile	Tyr	Phe	Tyr	Val	Thr	Thr	Ile	Pro	Asp	Gly	Phe	Thr	Ile						
545				550						555						560					
Glu	Ser	Lys	Pro	Ser	Glu	Glu	Leu	Leu	Glu	Gly	Gln	Pro	Val	Leu	Leu						
				565						570						575					
Ser	Cys	Gln	Ala	Asp	Ser	Tyr	Lys	Tyr	Glu	His	Leu	Arg	Trp	Tyr	Arg						
				580						585						590					
Leu	Asn	Leu	Ser	Thr	Leu	His	Asp	Ala	His	Gly	Asn	Pro	Leu	Leu	Leu						
				595						600						605					
Asp	Cys	Lys	Asn	Val	His	Leu	Phe	Ala	Thr	Pro	Leu	Ala	Ala	Ser	Leu						
				610						615						620					
Glu	Glu	Val	Ala	Pro	Gly	Ala	Arg	His	Ala	Thr	Leu	Ser	Leu	Ser	Ile						
625				630						635						640					
Pro	Arg	Val	Ala	Pro	Glu	His	Glu	Gly	His	Tyr	Val	Cys	Glu	Val	Gln						
				645						650						655					
Asp	Arg	Arg	Ser	His	Asp	Lys	His	Cys	His	Lys	Lys	Tyr	Leu	Ser	Val						
				660						665						670					
Gln	Ala	Leu	Glu	Ala	Pro	Arg	Leu	Thr	Gln	Asn	Leu	Thr	Asp	Leu	Leu						
				675						680						685					
Val	Asn	Val	Ser	Asp	Ser	Leu	Glu	Met	Gln	Cys	Leu	Val	Ala	Gly	Ala						
				690						695						700					
His	Ala	Pro	Ser	Ile	Val	Trp	Tyr	Lys	Asp	Glu	Arg	Leu	Leu	Glu	Glu						
705				710						715						720					
Lys	Ser	Gly	Val	Asp	Leu	Ala	Asp	Ser	Asn	Gln	Lys	Leu	Ser	Ile	Gln						
				725						730						735					
Arg	Val	Arg	Glu	Asp	Ala	Gly	Pro	Tyr	Leu	Cys	Ser	Val	Cys	Arg							
				740						745						750					
Pro	Lys	Gly	Cys	Val	Asn	Ser	Ser	Ala	Ser	Val	Ala	Val	Glu	Gly	Ser						
				755						760						765					
Glu	Asp	Lys	Gly	Ser	Met	Glu	Ile	Val	Ile	Leu	Val	Gly	Thr	Gly	Val						
				770						775						780					
Ile	Ala	Val	Phe	Phe	Trp	Val	Leu	Leu	Leu	Leu	Phe	Cys	Asn	Met							
785				790						795						800					
Arg	Arg	Pro	Ala	His	Ala	Asp	Ile	Lys	Thr	Gly	Tyr	Leu	Ser	Ile	Ile						
				805						810						815					
Met	Asp	Pro	Gly	Glu	Val	Pro	Leu	Glu	Gln	Cys	Glu	Tyr	Leu	Ser							
				820						825						830					
Tyr	Asp	Ala	Ser	Gln	Trp	Glu	Phe	Pro	Arg	Glu	Arg	Leu	His</								

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865					870					875				880	
Leu	Lys	Glu	Gly	Ala	Thr	Ala	Ser	Glu	Gln	Arg	Ala	Leu	Met	Ser	Glu
				885					890					895	
Leu	Lys	Ile	Leu	Ile	His	Ile	Gly	Asn	His	Leu	Asn	Val	Val	Asn	Leu
			900					905					910		
Leu	Gly	Ala	Cys	Thr	Lys	Pro	Gln	Gly	Pro	Leu	Met	Val	Ile	Val	Glu
		915					920					925			
Phe	Cys	Lys	Tyr	Gly	Asn	Leu	Ser	Asn	Phe	Leu	Arg	Ala	Lys	Arg	Asp
		930				935					940				
Ala	Phe	Ser	Pro	Cys	Ala	Glu	Lys	Ser	Pro	Glu	Gln	Arg	Gly	Arg	Phe
945					950					955					960
Arg	Ala	Met	Val	Glu	Leu	Ala	Arg	Leu	Asp	Arg	Arg	Arg	Pro	Gly	Ser
			965						970					975	
Ser	Asp	Arg	Val	Leu	Phe	Ala	Arg	Phe	Ser	Lys	Thr	Glu	Gly	Gly	Ala
			980					985					990		
Arg	Arg	Ala	Ser	Pro	Asp	Gln	Glu	Ala	Glu	Asp	Leu	Trp	Leu	Ser	Pro
		995				1000						1005			
Leu	Thr	Met	Glu	Asp	Leu	Val	Cys	Tyr	Ser	Phe	Gln	Val	Ala	Arg	Gly
	1010					1015					1020				
Met	Glu	Phe	Leu	Ala	Ser	Arg	Lys	Cys	Ile	His	Arg	Asp	Leu	Ala	Ala
1025					1030					1035					1040
Arg	Asn	Ile	Leu	Leu	Ser	Glu	Ser	Asp	Val	Val	Lys	Ile	Cys	Asp	Phe
			1045						1050					1055	
Gly	Leu	Ala	Arg	Asp	Ile	Tyr	Lys	Asp	Pro	Asp	Tyr	Val	Arg	Lys	Gly
		1060						1065					1070		
Ser	Ala	Arg	Leu	Pro	Leu	Lys	Trp	Met	Ala	Pro	Glu	Ser	Ile	Phe	Asp
		1075					1080					1085			
Lys	Val	Tyr	Thr	Thr	Gln	Ser	Asp	Val	Trp	Ser	Phe	Gly	Val	Leu	Leu
	1090					1095					1100				
Trp	Glu	Ile	Phe	Ser	Leu	Gly	Ala	Ser	Pro	Tyr	Pro	Gly	Val	Gln	Ile
1105					1110					1115					1120
Asn	Glu	Glu	Phe	Cys	Gln	Arg	Val	Arg	Asp	Gly	Thr	Arg	Met	Arg	Ala
			1125						1130					1135	
Pro	Glu	Leu	Ala	Thr	Pro	Ala	Ile	Arg	His	Ile	Met	Leu	Asn	Cys	Trp
		1140						1145					1150		
Ser	Gly	Asp	Pro	Lys	Ala	Arg	Pro	Ala	Phe	Ser	Glu	Leu	Val	Glu	Ile
		1155					1160					1165			
Leu	Gly	Asp	Leu	Leu	Gln	Gly	Arg	Gly	Leu	Gln	Glu	Glu	Glu	Glu	Val
	1170				1175					1180					
Cys	Met	Ala	Pro	Arg	Ser	Ser	Gln	Ser	Ser	Glu	Glu	Gly	Ser	Phe	Ser
1185					1190					1195					1200
Gln	Val	Ser	Thr	Met	Ala	Leu	His	Ile	Ala	Gln	Ala	Asp	Ala	Glu	Asp
			1205						1210					1215	
Ser	Pro	Pro	Ser	Leu	Gln	Arg	His	Ser	Leu	Ala	Ala	Arg	Tyr	Tyr	Asn
		1220						1225					1230		
Trp	Val	Ser	Phe	Pro	Gly	Cys	Leu	Ala	Arg	Gly	Ala	Glu	Thr	Arg	Gly
		1235					1240					1245			
Ser	Ser	Arg	Met	Lys	Thr	Phe	Glu	Glu	Phe	Pro	Met	Thr	Pro	Thr	Thr
		1250				1255					1260				
Tyr	Lys	Gly	Ser	Val	Asp	Asn	Gln	Thr	Asp	Ser	Gly	Met	Val	Leu	Ala
1265					1270					1275					1280
Ser	Glu	Glu	Phe	Glu	Gln	Ile	Glu	Ser	Arg	His	Arg	Gln	Glu	Ser	Gly
			1285						1290					1295	
Phe	Ser	Cys	Lys	Gly	Pro	Gly	Gln	Asn	Val	Ala	Val	Thr	Arg	Ala	His
		1300						1305				1310			
Pro	Asp	Ser	Gln	Gly	Arg	Arg	Arg	Arg	Pro	Glu	Arg	Gly	Ala	Arg	Gly

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1315                      1320                      1325  
 Gly Gln Val Phe Tyr Asn Ser Glu Tyr Gly Glu Leu Ser Glu Pro Ser  
 1330                      1335                      1340  
 Glu Glu Asp His Cys Ser Pro Ser Ala Arg Val Thr Phe Phe Thr Asp  
 1345                      1350                      1355                      1360  
 Asn Ser Tyr

<210> 274  
 <211> 1390  
 <212> PRT  
 <213> Homo sapiens

<300>  
 <308> GenBank No. NP000236  
 <309> 2004-10-28

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 20                      25                      30  
 Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala  
 35                      40                      45  
 Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu  
 50                      55                      60  
 Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys  
 65                      70                      75                      80  
 Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe  
 85                      90                      95  
 Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp  
 100                      105                      110  
 Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp  
 115                      120                      125  
 Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His  
 130                      135                      140  
 Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys  
 145                      150                      155                      160  
 Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val  
 165                      170                      175  
 Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe  
 180                      185                      190  
 Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp  
 195                      200                      205  
 His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp  
 210                      215                      220  
 Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu  
 225                      230                      235                      240  
 Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn  
 245                      250                      255  
 Asn Phe Ile Tyr Phe Leu Thr Val Gln Arg Glu Thr Leu Asp Ala Gln  
 260                      265                      270  
 Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Ile Asn Ser Gly Leu  
 275                      280                      285  
 His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg

	290					295					300						
Lys 305	Lys	Arg	Ser	Thr	Lys 310	Lys	Glu	Val	Phe	Asn 315	Ile	Leu	Gln	Ala	Ala 320		
Tyr	Val	Ser	Lys	Pro	Gly 325	Ala	Gln	Leu	Ala	Arg	Gln	Ile	Gly	Ala 335	Ser		
Leu	Asn	Asp	Asp	Ile	Leu	Phe	Gly	Val	Phe	Ala	Gln	Ser	Lys	Pro	Asp		
Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser	Ala	Met	Cys	Ala	Phe	Pro	Ile	Lys		
Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys	Ile	Val	Asn	Lys	Asn	Asn	Val	Arg		
Cys 385	Leu	Gln	His	Phe	Tyr 390	Gly	Pro	Asn	His	Glu	His	Cys	Phe	Asn	Arg 400		
Thr	Leu	Leu	Arg	Asn	Ser	Ser	Gly	Cys	Glu	Ala	Arg	Arg	Asp	Glu	Tyr 415		
Arg	Thr	Glu	Phe	Thr	Thr	Ala	Leu	Gln	Arg	Val	Asp	Leu	Phe	Met	Gly		
Gln	Phe	Ser	Glu	Val	Leu	Leu	Thr	Ser	Ile	Ser	Thr	Phe	Ile	Lys	Gly		
Asp	Leu	Thr	Ile	Ala	Asn	Leu	Gly	Thr	Ser	Glu	Gly	Arg	Phe	Met	Gln		
Val 465	Val	Val	Ser	Arg	Ser	Gly	Pro	Ser	Thr	Pro	His	Val	Asn	Phe	Leu 480		
Leu	Asp	Ser	His	Pro	Val	Ser	Pro	Glu	Val	Ile	Val	Glu	His	Thr	Leu		
Asn	Gln	Asn	Gly	Tyr	Thr	Leu	Val	Ile	Thr	Gly	Lys	Lys	Ile	Thr	Lys		
Ile	Pro	Leu	Asn	Gly	Leu	Gly	Cys	Arg	His	Phe	Gln	Ser	Cys	Ser	Gln		
Cys	Leu	Ser	Ala	Pro	Pro	Phe	Val	Gln	Cys	Gly	Trp	Cys	His	Asp	Lys		
Cys 545	Val	Arg	Ser	Glu	Glu	Cys	Leu	Ser	Gly	Thr	Trp	Thr	Gln	Gln	Ile 560		
Cys	Leu	Pro	Ala	Ile	Tyr	Lys	Val	Phe	Pro	Asn	Ser	Ala	Pro	Leu	Glu		
Gly	Gly	Thr	Arg	Leu	Thr	Ile	Cys	Gly	Trp	Asp	Phe	Gly	Phe	Arg	Arg		
Asn	Asn	Lys	Phe	Asp	Leu	Lys	Lys	Thr	Arg	Val	Leu	Leu	Gly	Asn	Glu		
Ser	Cys	Thr	Leu	Thr	Leu	Ser	Glu	Ser	Thr	Met	Asn	Thr	Leu	Lys	Cys		
Thr 625	Val	Gly	Pro	Ala	Met	Asn	Lys	His	Phe	Asn	Met	Ser	Ile	Ile	Ile 640		
Ser	Asn	Gly	His	Gly	Thr	Thr	Gln	Tyr	Ser	Thr	Phe	Ser	Tyr	Val	Asp		
Pro	Val	Ile	Thr	Ser	Ile	Ser	Pro	Lys	Tyr	Gly	Pro	Met	Ala	Gly	Gly		
Thr	Leu	Leu	Thr	Leu	Thr	Gly	Asn	Tyr	Leu	Asn	Ser	Gly	Asn	Ser	Arg		
His	Ile	Ser	Ile	Gly	Gly	Lys	Thr	Cys	Thr	Leu	Lys	Ser	Val	Ser	Asn		
Ser 705	Ile	Leu	Glu	Cys	Tyr	Thr	Pro	Ala	Gln	Thr	Ile	Ser	Thr	Glu	Phe 720		
Ala	Val	Lys	Leu	Lys	Ile	Asp	Leu	Ala	Asn	Arg	Glu	Thr	Ser	Ile	Phe		
Ser	Tyr	Arg	Glu	Asp	Pro	Ile	Val	Tyr	Glu	Ile	His	Pro	Thr	Lys	Ser		

			740					745				750			
Phe	Ile	Ser	Gly	Gly	Ser	Thr	Ile	Thr	Gly	Val	Gly	Lys	Asn	Leu	Asn
		755					760				765				
Ser	Val	Ser	Val	Pro	Arg	Met	Val	Ile	Asn	Val	His	Glu	Ala	Gly	Arg
	770					775				780					
Asn	Phe	Thr	Val	Ala	Cys	Gln	His	Arg	Ser	Asn	Ser	Glu	Ile	Ile	Cys
785				790					795						800
Cys	Thr	Thr	Pro	Ser	Leu	Gln	Gln	Leu	Asn	Leu	Gln	Leu	Pro	Leu	Lys
			805						810					815	
Thr	Lys	Ala	Phe	Phe	Met	Leu	Asp	Gly	Ile	Leu	Ser	Lys	Tyr	Phe	Asp
		820						825					830		
Leu	Ile	Tyr	Val	His	Asn	Pro	Val	Phe	Lys	Pro	Phe	Glu	Lys	Pro	Val
	835					840					845				
Met	Ile	Ser	Met	Gly	Asn	Glu	Asn	Val	Leu	Glu	Ile	Lys	Gly	Asn	Asp
	850					855					860				
Ile	Asp	Pro	Glu	Ala	Val	Lys	Gly	Glu	Val	Leu	Lys	Val	Gly	Asn	Lys
865				870						875					880
Ser	Cys	Glu	Asn	Ile	His	Leu	His	Ser	Glu	Ala	Val	Leu	Cys	Thr	Val
			885						890					895	
Pro	Asn	Asp	Leu	Leu	Lys	Leu	Asn	Ser	Glu	Leu	Asn	Ile	Glu	Trp	Lys
		900						905					910		
Gln	Ala	Ile	Ser	Ser	Thr	Val	Leu	Gly	Lys	Val	Ile	Val	Gln	Pro	Asp
	915						920					925			
Gln	Asn	Phe	Thr	Gly	Leu	Ile	Ala	Gly	Val	Val	Ser	Ile	Ser	Thr	Ala
	930					935					940				
Leu	Leu	Leu	Leu	Leu	Gly	Phe	Phe	Leu	Trp	Leu	Lys	Lys	Arg	Lys	Gln
945					950					955					960
Ile	Lys	Asp	Leu	Gly	Ser	Glu	Leu	Val	Arg	Tyr	Asp	Ala	Arg	Val	His
			965						970					975	
Thr	Pro	His	Leu	Asp	Arg	Leu	Val	Ser	Ala	Arg	Ser	Val	Ser	Pro	Thr
		980						985					990		
Thr	Glu	Met	Val	Ser	Asn	Glu	Ser	Val	Asp	Tyr	Arg	Ala		Phe	Pro
	995						1000					1005			
Glu	Asp	Gln	Phe	Pro	Asn	Ser	Ser	Gln	Asn	Gly	Ser	Cys	Arg	Gln	Val
	1010					1015					1020				
Gln	Tyr	Pro	Leu	Thr	Asp	Met	Ser	Pro	Ile	Leu	Thr	Ser	Gly	Asp	Ser
1025					1030					1035					1040
Asp	Ile	Ser	Ser	Pro	Leu	Leu	Gln	Asn	Thr	Val	His	Ile	Asp	Leu	Ser
			1045						1050					1055	
Ala	Leu	Asn	Pro	Glu	Leu	Val	Gln	Ala	Val	Gln	His	Val	Val	Ile	Gly
		1060						1065					1070		
Pro	Ser	Ser	Leu	Ile	Val	His	Phe	Asn	Glu	Val	Ile	Gly	Arg	Gly	His
		1075					1080					1085			
Phe	Gly	Cys	Val	Tyr	His	Gly	Thr	Leu	Leu	Asp	Asn	Asp	Gly	Lys	Lys

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1185              1190              1195              1200
Val His Arg Asp Leu Ala Ala Arg Asn Cys Met Leu Asp Glu Lys Phe
              1205              1210              1215
Thr Val Lys Val Ala Asp Phe Gly Leu Ala Arg Asp Met Tyr Asp Lys
              1220              1225              1230
Glu Tyr Tyr Ser Val His Asn Lys Thr Gly Ala Lys Leu Pro Val Lys
              1235              1240              1245
Trp Met Ala Leu Glu Ser Leu Gln Thr Gln Lys Phe Thr Thr Lys Ser
              1250              1255              1260
Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Leu Met Thr Arg Gly
1265              1270              1275              1280
Ala Pro Pro Tyr Pro Asp Val Asn Thr Phe Asp Ile Thr Val Tyr Leu
              1285              1290              1295
Leu Gln Gly Arg Arg Leu Leu Gln Pro Glu Tyr Cys Pro Asp Pro Leu
              1300              1305              1310
Tyr Glu Val Met Leu Lys Cys Trp His Pro Lys Ala Glu Met Arg Pro
              1315              1320              1325
Ser Phe Ser Glu Leu Val Ser Arg Ile Ser Ala Ile Phe Ser Thr Phe
              1330              1335              1340
Ile Gly Glu His Tyr Val His Val Asn Ala Thr Tyr Val Asn Val Lys
1345              1350              1355              1360
Cys Val Ala Pro Tyr Pro Ser Leu Leu Ser Ser Glu Asp Asn Ala Asp
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Asp Glu Val Asp Thr Arg Pro Ala Ser Phe Trp Glu Thr Ser
              1380              1385              1390

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<210> 275  
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 <212> PRT  
 <213> Homo sapiens

<300>  
 <308> GenBank No. NP006197  
 <309> 2004-10-26

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Asn Glu Asn Glu Lys Val Val Gln Leu Asn Ser Ser Phe Ser Leu Arg
 35      40      45
Cys Phe Gly Glu Ser Glu Val Ser Trp Gln Tyr Pro Met Ser Glu Glu
 50      55      60
Glu Ser Ser Asp Val Glu Ile Arg Asn Glu Glu Asn Asn Ser Gly Leu
 65      70      75      80
Phe Val Thr Val Leu Glu Val Ser Ser Ala Ser Ala Ala His Thr Gly
 85      90      95
Leu Tyr Thr Cys Tyr Tyr Asn His Thr Gln Thr Glu Glu Asn Glu Leu
100      105      110
Glu Gly Arg His Ile Tyr Ile Tyr Val Pro Asp Pro Asp Val Ala Phe
115      120      125
Val Pro Leu Gly Met Thr Asp Tyr Leu Val Ile Val Glu Asp Asp Asp
130      135      140
Ser Ala Ile Ile Pro Cys Arg Thr Thr Asp Pro Glu Thr Pro Val Thr

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145					150					155				160
Leu	His	Asn	Ser	Glu	Gly	Val	Val	Pro	Ala	Ser	Tyr	Asp	Ser	Arg
				165					170					175
Gly	Phe	Asn	Gly	Thr	Phe	Thr	Val	Gly	Pro	Tyr	Ile	Cys	Glu	Ala
			180					185					190	
Val	Lys	Gly	Lys	Lys	Phe	Gln	Thr	Ile	Pro	Phe	Asn	Val	Tyr	Ala
		195					200					205		Leu
Lys	Ala	Thr	Ser	Glu	Leu	Asp	Leu	Glu	Met	Glu	Ala	Leu	Lys	Thr
	210					215				220				Val
Tyr	Lys	Ser	Gly	Glu	Thr	Ile	Val	Val	Thr	Cys	Ala	Val	Phe	Asn
225				230					235					240
Glu	Val	Val	Asp	Leu	Gln	Trp	Thr	Tyr	Pro	Gly	Glu	Val	Lys	Gly
			245					250					255	Lys
Gly	Ile	Thr	Met	Leu	Glu	Glu	Ile	Lys	Val	Pro	Ser	Ile	Lys	Leu
		260					265					270		Val
Tyr	Thr	Leu	Thr	Val	Pro	Glu	Ala	Thr	Val	Lys	Asp	Ser	Gly	Asp
	275					280						285		Tyr
Glu	Cys	Ala	Ala	Arg	Gln	Ala	Thr	Arg	Glu	Val	Lys	Glu	Met	Lys
	290				295					300				Lys
Val	Thr	Ile	Ser	Val	His	Glu	Lys	Gly	Phe	Ile	Glu	Ile	Lys	Pro
305				310					315					320
Phe	Ser	Gln	Leu	Glu	Ala	Val	Asn	Leu	His	Glu	Val	Lys	His	Phe
			325					330					335	Val
Val	Glu	Val	Arg	Ala	Tyr	Pro	Pro	Pro	Arg	Ile	Ser	Trp	Leu	Lys
	340						345					350		Asn
Asn	Leu	Thr	Leu	Ile	Glu	Asn	Leu	Thr	Glu	Ile	Thr	Thr	Asp	Val
	355					360					365			Glu
Lys	Ile	Gln	Glu	Ile	Arg	Tyr	Arg	Ser	Lys	Leu	Lys	Leu	Ile	Arg
	370				375				380					Ala
Lys	Glu	Glu	Asp	Ser	Gly	His	Tyr	Thr	Ile	Val	Ala	Gln	Asn	Glu
385				390					395					400
Ala	Val	Lys	Ser	Tyr	Thr	Phe	Glu	Leu	Leu	Thr	Gln	Val	Pro	Ser
			405					410				415		Ser
Ile	Leu	Asp	Leu	Val	Asp	Asp	His	His	Gly	Ser	Thr	Gly	Gly	Gln
		420					425					430		Thr
Val	Arg	Cys	Thr	Ala	Glu	Gly	Thr	Pro	Leu	Pro	Asp	Ile	Glu	Trp
	435					440					445			Met
Ile	Cys	Lys	Asp	Ile	Lys	Lys	Cys	Asn	Asn	Glu	Thr	Ser	Trp	Thr
	450				455					460				Ile
Leu	Ala	Asn	Asn	Val	Ser	Asn	Ile	Ile	Thr	Glu	Ile	His	Ser	Arg
465				470					475					480
Arg	Ser	Thr	Val	Glu	Gly	Arg	Val	Thr	Phe	Ala	Lys	Val	Glu	Glu
			485					490					495	Thr
Ile	Ala	Val	Arg	Cys	Leu	Ala	Lys	Asn	Leu	Leu	Gly	Ala	Glu	Asn
	500						505					510		Arg
Glu	Leu	Lys	Leu	Val	Ala	Pro	Thr	Leu	Arg	Ser	Glu	Leu	Thr	Val
	515					520					525			Ala
Ala	Ala	Val	Leu	Val	Leu	Leu	Val	Ile	Val	Ile	Ile	Ser	Leu	Ile
	530					535				540				Val
Leu	Val	Val	Ile	Trp	Lys	Gln	Lys	Pro	Arg	Tyr	Glu	Ile	Arg	Trp
545				550					555					560
Val	Ile	Glu	Ser	Ile	Ser	Pro	Asp	Gly	His	Glu	Tyr	Ile	Tyr	Val
			565					570					575	Asp
Pro	Met	Gln	Leu	Pro	Tyr	Asp	Ser	Arg	Trp	Glu	Phe	Pro	Arg	Asp
		580					585					590		Gly
Leu	Val	Leu	Gly	Arg	Val	Leu	Gly	Ser	Gly	Ala	Phe	Gly	Lys	Val

	595					600					605					
Glu 610	Gly	Thr	Ala	Tyr	Gly 615	Leu	Ser	Arg	Ser	Gln 620	Pro	Val	Met	Lys	Val	
Ala 625	Val	Lys	Met	Leu	Lys 630	Pro	Thr	Ala	Arg	Ser 635	Ser	Glu	Lys	Gln	Ala 640	
Leu	Met	Ser	Glu	Leu 645	Lys	Ile	Met	Thr	His 650	Leu	Gly	Pro	His	Leu	Asn 655	
Ile	Val	Asn	Leu 660	Leu	Gly	Ala	Cys	Thr 665	Lys	Ser	Gly	Pro	Ile 670	Tyr	Ile	
Ile	Thr	Glu 675	Tyr	Cys	Phe	Tyr	Gly 680	Asp	Leu	Val	Asn	Tyr 685	Leu	His	Lys	
Asn 690	Arg	Asp	Ser	Phe	Leu	Ser 695	His	His	Pro	Glu	Lys 700	Pro	Lys	Lys	Glu	
Leu 705	Asp	Ile	Phe	Gly	Leu 710	Asn	Pro	Ala	Asp	Glu 715	Ser	Thr	Arg	Ser	Tyr 720	
Val	Ile	Leu	Ser	Phe 725	Glu	Asn	Asn	Gly	Asp 730	Tyr	Met	Asp	Met	Lys	Gln 735	
Ala	Asp	Thr	Thr 740	Gln	Tyr	Val	Pro	Met	Leu 745	Glu	Arg	Lys	Glu 750	Val	Ser	
Lys	Tyr	Ser	Asp 755	Ile	Gln	Arg	Ser 760	Leu	Tyr	Asp	Arg	Pro 765	Ala	Ser	Tyr	
Lys 770	Lys	Lys	Ser	Met	Leu	Asp 775	Ser	Glu	Val	Lys	Asn	Leu 780	Leu	Ser	Asp	
Asp 785	Asn	Ser	Glu	Gly	Leu 790	Thr	Leu	Leu	Asp	Leu 795	Leu	Ser	Phe	Thr	Tyr 800	
Gln	Val	Ala	Arg	Gly 805	Met	Glu	Phe	Leu	Ala 810	Ser	Lys	Asn	Cys	Val	His 815	
Arg	Asp	Leu	Ala 820	Ala	Arg	Asn	Val	Leu	Leu 825	Ala	Gln	Gly	Lys 830	Ile	Val	
Lys	Ile	Cys	Asp 835	Phe	Gly	Leu	Ala 840	Arg	Asp	Ile	Met	His 845	Asp	Ser	Asn	
Tyr	Val	Ser	Lys	Gly	Ser	Thr 855	Phe	Leu	Pro	Val	Lys	Trp 860	Met	Ala	Pro	
Glu 865	Ser	Ile	Phe	Asp	Asn 870	Leu	Tyr	Thr	Thr	Leu 875	Ser	Asp	Val	Trp	Ser 880	
Tyr	Gly	Ile	Leu	Leu 885	Trp	Glu	Ile	Phe	Ser 890	Leu	Gly	Gly	Thr	Pro	Tyr 895	
Pro	Gly	Met	Met 900	Val	Asp	Ser	Thr	Phe	Tyr 905	Asn	Lys	Ile	Lys 910	Ser	Gly	
Tyr	Arg	Met	Ala 915	Lys	Pro	Asp	His 920	Ala	Thr	Ser	Glu	Val 925	Tyr	Glu	Ile	
Met	Val	Lys	Cys	Trp	Asn	Ser 935	Glu	Pro	Glu	Lys	Arg 940	Pro	Ser	Phe	Tyr	
His 945	Leu	Ser	Glu	Ile	Val 950	Glu	Asn	Leu	Leu	Pro 955	Gly	Gln	Tyr	Lys	Lys 960	
Ser	Tyr	Glu	Lys	Ile 965	His	Leu	Asp	Phe	Leu 970	Lys	Ser	Asp	His	Pro	Ala 975	
Val	Ala	Arg	Met 980	Arg	Val	Asp	Ser	Asp	Asn 985	Ala	Tyr	Ile	Gly 990	Val	Thr	
Tyr	Lys	Asn	Glu 995	Glu	Asp	Lys	Leu	Lys	Asp	Trp	Glu	Gly 1005	Gly	Leu	Asp	
Glu	Gln	Arg	Leu 1010	Ser	Ala	Asp	Ser	Gly	Tyr	Ile	Ile	Pro 1020	Leu	Pro	Asp	
Ile 1025	Asp	Pro	Val	Pro	Glu 1030	Glu	Glu	Asp	Leu	Gly	Lys	Arg	Asn	Arg	His 1040	
Ser	Ser	Gln	Thr	Ser	Glu	Glu	Ser	Ala	Ile	Glu	Thr	Gly	Ser	Ser	Ser	

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				1045					1050				1055
Ser	Thr	Phe	Ile	Lys	Arg	Glu	Asp	Glu	Thr	Ile	Glu	Asp	Ile
				1060				1065					1070
Met	Asp	Asp	Ile	Gly	Ile	Asp	Ser	Ser	Asp	Leu	Val	Glu	Asp
				1075			1080					1085	Ser
													Phe
Leu													

<210> 276  
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 <213> Homo sapiens

<300>  
 <308> GenBank No. NP002600  
 <309> 2004-10-26

<400> 276

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			20				25					30			
Leu	Val	Val	Thr	Pro	Pro	Gly	Pro	Glu	Leu	Val	Leu	Asn	Val	Ser	Ser
			35				40					45			
Thr	Phe	Val	Leu	Thr	Cys	Ser	Gly	Ser	Ala	Pro	Val	Val	Trp	Glu	Arg
			50			55					60				
Met	Ser	Gln	Glu	Pro	Pro	Gln	Glu	Met	Ala	Lys	Ala	Gln	Asp	Gly	Thr
65				70					75					80	
Phe	Ser	Ser	Val	Leu	Thr	Leu	Thr	Asn	Leu	Thr	Gly	Leu	Asp	Thr	Gly
			85					90					95		
Glu	Tyr	Phe	Cys	Thr	His	Asn	Asp	Ser	Arg	Gly	Leu	Glu	Thr	Asp	Glu
			100				105						110		
Arg	Lys	Arg	Leu	Tyr	Ile	Phe	Val	Pro	Asp	Pro	Thr	Val	Gly	Phe	Leu
			115				120					125			
Pro	Asn	Asp	Ala	Glu	Glu	Leu	Phe	Ile	Phe	Leu	Thr	Glu	Ile	Thr	Glu
			130			135					140				
Ile	Thr	Ile	Pro	Cys	Arg	Val	Thr	Asp	Pro	Gln	Leu	Val	Val	Thr	Leu
145				150					155						160
His	Glu	Lys	Lys	Gly	Asp	Val	Ala	Leu	Pro	Val	Pro	Tyr	Asp	His	Gln
			165					170					175		
Arg	Gly	Phe	Ser	Gly	Ile	Phe	Glu	Asp	Arg	Ser	Tyr	Ile	Cys	Lys	Thr
			180				185						190		
Thr	Ile	Gly	Asp	Arg	Glu	Val	Asp	Ser	Asp	Ala	Tyr	Tyr	Val	Tyr	Arg
			195				200					205			
Leu	Gln	Val	Ser	Ser	Ile	Asn	Val	Ser	Val	Asn	Ala	Val	Gln	Thr	Val
			210			215				220					
Val	Arg	Gln	Gly	Glu	Asn	Ile	Thr	Leu	Met	Cys	Ile	Val	Ile	Gly	Asn
225				230					235						240
Glu	Val	Val	Asn	Phe	Glu	Trp	Thr	Tyr	Pro	Arg	Lys	Glu	Ser	Gly	Arg
			245					250					255		
Leu	Val	Glu	Pro	Val	Thr	Asp	Phe	Leu	Leu	Asp	Met	Pro	Tyr	His	Ile
			260				265						270		
Arg	Ser	Ile	Leu	His	Ile	Pro	Ser	Ala	Glu	Leu	Glu	Asp	Ser	Gly	Thr
			275			280						285			
Tyr	Thr	Cys	Asn	Val	Thr	Glu	Ser	Val	Asn	Asp	His	Gln	Asp	Glu	Lys

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290	295	300
Ala Ile Asn Ile Thr Val Val Glu Ser Gly Tyr Val Arg Leu Leu Gly		
305	310	315
Glu Val Gly Thr Leu Gln Phe Ala Glu Leu His Arg Ser Arg Thr Leu		
	325	330
Gln Val Val Phe Glu Ala Tyr Pro Pro Thr Val Leu Trp Phe Lys		335
	340	345
Asp Asn Arg Thr Leu Gly Asp Ser Ser Ala Gly Glu Ile Ala Leu Ser		350
	355	360
Thr Arg Asn Val Ser Glu Thr Arg Tyr Val Ser Glu Leu Thr Leu Val		365
	370	375
Arg Val Lys Val Ala Glu Ala Gly His Tyr Thr Met Arg Ala Phe His		380
385	390	395
Glu Asp Ala Glu Val Gln Leu Ser Phe Gln Leu Gln Ile Asn Val Pro		400
	405	410
Val Arg Val Leu Glu Leu Ser Glu Ser His Pro Asp Ser Gly Glu Gln		415
	420	425
Thr Val Arg Cys Arg Gly Arg Gly Met Pro Gln Pro Asn Ile Ile Trp		430
	435	440
Ser Ala Cys Arg Asp Leu Lys Arg Cys Pro Arg Glu Leu Pro Pro Thr		445
	450	455
Leu Leu Gly Asn Ser Ser Glu Glu Ser Gln Leu Glu Thr Asn Val		460
465	470	475
Thr Tyr Trp Glu Glu Glu Gln Glu Phe Glu Val Val Ser Thr Leu Arg		480
	485	490
Leu Gln His Val Asp Arg Pro Leu Ser Val Arg Cys Thr Leu Arg Asn		495
	500	505
Ala Val Gly Gln Asp Thr Gln Glu Val Ile Val Val Pro His Ser Leu		510
	515	520
Pro Phe Lys Val Val Val Ile Ser Ala Ile Leu Ala Leu Val Val Leu		525
	530	535
Thr Ile Ile Ser Leu Ile Ile Leu Ile Met Leu Trp Gln Lys Lys Pro		540
545	550	555
Arg Tyr Glu Ile Arg Trp Lys Val Ile Glu Ser Val Ser Ser Asp Gly		560
	565	570
His Glu Tyr Ile Tyr Val Asp Pro Met Gln Leu Pro Tyr Asp Ser Thr		575
	580	585
Trp Glu Leu Pro Arg Asp Gln Leu Val Leu Gly Arg Thr Leu Gly Ser		590
	595	600
Gly Ala Phe Gly Gln Val Val Glu Ala Thr Ala His Gly Leu Ser His		605
	610	615
Ser Gln Ala Thr Met Lys Val Ala Val Lys Met Leu Lys Ser Thr Ala		620
625	630	635
Arg Ser Ser Glu Lys Gln Ala Leu Met Ser Glu Leu Lys Ile Met Ser		640
	645	650
His Leu Gly Pro His Leu Asn Val Val Asn Leu Leu Gly Ala Cys Thr		655
	660	665
Lys Gly Gly Pro Ile Tyr Ile Ile Thr Glu Tyr Cys Arg Tyr Gly Asp		670
	675	680
Leu Val Asp Tyr Leu His Arg Asn Lys His Thr Phe Leu Gln His His		685
	690	695
Ser Asp Lys Arg Arg Pro Ser Ala Glu Leu Tyr Ser Asn Ala Leu		700
705	710	715
Pro Val Gly Leu Pro Leu Pro Ser His Val Ser Leu Thr Gly Glu Ser		720
	725	730
Asp Gly Gly Tyr Met Asp Met Ser Lys Asp Glu Ser Val Asp Tyr Val		735

[illegible]

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<210> 277
<211> 1400
<212> PRT
<213> Homo sapiens

<300>
<308> GenBank No. NP002438
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&lt;309&gt; 2004-10-28

&lt;400&gt; 277

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Met Glu Leu Leu Pro Pro Leu Pro Gln Ser Phe Leu Leu Leu Leu Leu
 1          5          10          15
Leu Pro Ala Lys Pro Ala Ala Gly Glu Asp Trp Gln Cys Pro Arg Thr
 20          25          30
Pro Tyr Ala Ala Ser Arg Asp Phe Asp Val Lys Tyr Val Val Pro Ser
 35          40          45
Phe Ser Ala Gly Gly Leu Val Gln Ala Met Val Thr Tyr Glu Gly Asp
 50          55          60
Arg Asn Glu Ser Ala Val Phe Val Ala Ile Arg Asn Arg Leu His Val
 65          70          75          80
Leu Gly Pro Asp Leu Lys Ser Val Gln Ser Leu Ala Thr Gly Pro Ala
 85          90          95
Gly Asp Pro Gly Cys Gln Thr Cys Ala Ala Cys Gly Pro Gly Pro His
 100          105          110
Gly Pro Pro Gly Asp Thr Asp Thr Lys Val Leu Val Leu Asp Pro Ala
 115          120          125
Leu Pro Ala Leu Val Ser Cys Gly Ser Ser Leu Gln Gly Arg Cys Phe
 130          135          140
Leu His Asp Leu Glu Pro Gln Gly Thr Ala Val His Leu Ala Ala Pro
 145          150          155          160
Ala Cys Leu Phe Ser Ala His His Asn Arg Pro Asp Asp Cys Pro Asp
 165          170          175
Cys Val Ala Ser Pro Leu Gly Thr Arg Val Thr Val Val Glu Gln Gly
 180          185          190
Gln Ala Ser Tyr Phe Tyr Val Ala Ser Ser Leu Asp Ala Ala Val Ala
 195          200          205
Gly Ser Phe Ser Pro Arg Ser Val Ser Ile Arg Arg Leu Lys Ala Asp
 210          215          220
Ala Ser Gly Phe Ala Pro Gly Phe Val Ala Leu Ser Val Leu Pro Lys
 225          230          235          240
His Leu Val Ser Tyr Ser Ile Glu Tyr Val His Ser Phe His Thr Gly
 245          250          255
Ala Phe Val Tyr Phe Leu Thr Val Gln Pro Ala Ser Val Thr Asp Asp
 260          265          270
Pro Ser Ala Leu His Thr Arg Leu Ala Arg Leu Ser Ala Thr Glu Pro
 275          280          285
Glu Leu Gly Asp Tyr Arg Glu Leu Val Leu Asp Cys Arg Phe Ala Pro
 290          295          300
Lys Arg Arg Arg Arg Gly Ala Pro Glu Gly Gly Gln Pro Tyr Pro Val
 305          310          315          320
Leu Gln Val Ala His Ser Ala Pro Val Gly Ala Gln Leu Ala Thr Glu
 325          330          335
Leu Ser Ile Ala Glu Gly Gln Glu Val Leu Phe Gly Val Phe Val Thr
 340          345          350
Gly Lys Asp Gly Gly Pro Gly Val Gly Pro Asn Ser Val Val Cys Ala
 355          360          365
Phe Pro Ile Asp Leu Leu Asp Thr Leu Ile Asp Glu Gly Val Glu Arg
 370          375          380
Cys Cys Glu Ser Pro Val His Pro Gly Leu Arg Arg Gly Leu Asp Phe
 385          390          395          400
Phe Gln Ser Pro Ser Phe Cys Pro Asn Pro Pro Gly Leu Glu Ala Leu
 405          410          415
Ser Pro Asn Thr Ser Cys Arg His Phe Pro Leu Leu Val Ser Ser Ser

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			420					425					430				
Phe	Ser	Arg	Val	Asp	Leu	Phe	Asn	Gly	Leu	Leu	Gly	Pro	Val	Gln	Val		
		435					440					445					
Thr	Ala	Leu	Tyr	Val	Thr	Arg	Leu	Asp	Asn	Val	Thr	Val	Ala	His	Met		
		450					455					460					
Gly	Thr	Met	Asp	Gly	Arg	Ile	Leu	Gln	Val	Glu	Leu	Val	Arg	Ser	Leu		
465					470					475					480		
Asn	Tyr	Leu	Leu	Tyr	Val	Ser	Asn	Phe	Ser	Leu	Gly	Asp	Ser	Gly	Gln		
				485					490					495			
Pro	Val	Gln	Arg	Asp	Val	Ser	Arg	Leu	Gly	Asp	His	Leu	Leu	Phe	Ala		
			500					505				510					
Ser	Gly	Asp	Gln	Val	Phe	Gln	Val	Pro	Ile	Arg	Gly	Pro	Gly	Cys	Arg		
		515					520					525					
His	Phe	Leu	Thr	Cys	Gly	Arg	Cys	Leu	Arg	Ala	Trp	His	Phe	Met	Gly		
	530					535				540							
Cys	Gly	Trp	Cys	Gly	Asn	Met	Cys	Gly	Gln	Gln	Lys	Glu	Cys	Pro	Gly		
545					550					555					560		
Ser	Trp	Gln	Gln	Asp	His	Cys	Pro	Pro	Lys	Leu	Thr	Glu	Phe	His	Pro		
				565					570					575			
His	Ser	Gly	Pro	Leu	Arg	Gly	Ser	Thr	Arg	Leu	Thr	Leu	Cys	Gly	Ser		
		580						585					590				
Asn	Phe	Tyr	Leu	His	Pro	Ser	Gly	Leu	Val	Pro	Glu	Gly	Thr	His	Gln		
		595					600					605					
Val	Thr	Val	Gly	Gln	Ser	Pro	Cys	Arg	Pro	Leu	Pro	Lys	Asp	Ser	Ser		
	610					615					620						
Lys	Leu	Arg	Pro	Val	Pro	Arg	Lys	Asp	Phe	Val	Glu	Glu	Phe	Glu	Cys		
625					630					635					640		
Glu	Leu	Glu	Pro	Leu	Gly	Thr	Gln	Ala	Val	Gly	Pro	Thr	Asn	Val	Ser		
				645					650					655			
Leu	Thr	Val	Thr	Asn	Met	Pro	Pro	Gly	Lys	His	Phe	Arg	Val	Asp	Gly		
		660						665					670				
Thr	Ser	Val	Leu	Arg	Gly	Phe	Ser	Phe	Met	Glu	Pro	Val	Leu	Ile	Ala		
		675					680					685					
Val	Gln	Pro	Leu	Phe	Gly	Pro	Arg	Ala	Gly	Gly	Thr	Cys	Leu	Thr	Leu		
	690					695					700						
Glu	Gly	Gln	Ser	Leu	Ser	Val	Gly	Thr	Ser	Arg	Ala	Val	Leu	Val	Asn		
705					710					715					720		
Gly	Thr	Glu	Cys	Leu	Leu	Ala	Arg	Val	Ser	Glu	Gly	Gln	Leu	Leu	Cys		
				725					730					735			
Ala	Thr	Pro	Pro	Gly	Ala	Thr	Val	Ala	Ser	Val	Pro	Leu	Ser	Leu	Gln		
			740					745					750				
Val	Gly	Gly	Ala	Gln	Val	Pro	Gly	Ser	Trp	Thr	Phe	Gln	Tyr	Arg	Glu		
		755					760					765					
Asp	Pro	Val	Val	Leu	Ser	Ile	Ser	Pro	Asn	Cys	Gly	Tyr	Ile	Asn	Ser		
		770				775					780						
His	Ile	Thr	Ile	Cys	Gly	Gln	His	Leu	Thr	Ser	Ala	Trp	His	Leu	Val		
785					790					795					800		
Leu	Ser	Phe	His	Asp	Gly	Leu	Arg	Ala	Val	Glu	Ser	Arg	Cys	Glu	Arg		
				805					810					815			
Gln	Leu	Pro	Glu	Gln	Gln	Leu	Cys	Arg	Leu	Pro	Glu	Tyr	Val	Val	Arg		
				820				825					830				
Asp	Pro	Gln	Gly	Trp	Val	Ala	Gly	Asn	Leu	Ser	Ala	Arg	Gly	Asp	Gly		
		835					840					845					
Ala	Ala	Gly	Phe	Thr	Leu	Pro	Gly	Phe	Arg	Phe	Leu	Pro	Pro	Pro	His		
	850					855					860						
Pro	Pro	Ser	Ala	Asn	Leu	Val	Pro	Leu	Lys	Pro	Glu	Glu	His	Ala	Ile		

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865					870					875				880
Lys	Phe	Glu	Tyr	Ile	Gly	Leu	Gly	Ala	Val	Ala	Asp	Cys	Val	Gly Ile
				885					890					895
Asn	Val	Thr	Val	Gly	Gly	Glu	Ser	Cys	Gln	His	Glu	Phe	Arg	Gly Asp
			900					905					910	
Met	Val	Val	Cys	Pro	Leu	Pro	Pro	Ser	Leu	Gln	Leu	Gly	Gln	Asp Gly
		915					920					925		
Ala	Pro	Leu	Gln	Val	Cys	Val	Asp	Gly	Glu	Cys	His	Ile	Leu	Gly Arg
	930					935					940			
Val	Val	Arg	Pro	Gly	Pro	Asp	Gly	Val	Pro	Gln	Ser	Thr	Leu	Leu Gly
945				950					955					960
Ile	Leu	Leu	Pro	Leu	Leu	Leu	Val	Ala	Ala	Leu	Ala	Thr	Ala	Leu
			965					970						975
Val	Phe	Ser	Tyr	Trp	Trp	Arg	Arg	Lys	Gln	Leu	Val	Leu	Pro	Pro Asn
			980					985					990	
Leu	Asn	Asp	Leu	Ala	Ser	Leu	Asp	Gln	Thr	Ala	Gly	Ala	Thr	Pro Leu
	995						1000					1005		
Pro	Ile	Leu	Tyr	Ser	Gly	Ser	Asp	Tyr	Arg	Ser	Gly	Leu	Ala	Leu Pro
	1010					1015					1020			
Ala	Ile	Asp	Gly	Leu	Asp	Ser	Thr	Thr	Cys	Val	His	Gly	Ala	Ser Phe
1025				1030						1035				1040
Ser	Asp	Ser	Glu	Asp	Glu	Ser	Cys	Val	Pro	Leu	Leu	Arg	Lys	Glu Ser
			1045						1050					1055
Ile	Gln	Leu	Arg	Asp	Leu	Asp	Ser	Ala	Leu	Leu	Ala	Glu	Val	Lys Asp
			1060					1065						1070
Val	Leu	Ile	Pro	His	Glu	Arg	Val	Val	Thr	His	Ser	Asp	Arg	Val Ile
	1075						1080					1085		
Gly	Lys	Gly	His	Phe	Gly	Val	Val	Tyr	His	Gly	Glu	Tyr	Ile	Asp Gln
	1090				1095					1100				
Ala	Gln	Asn	Arg	Ile	Gln	Cys	Ala	Ile	Lys	Ser	Leu	Ser	Arg	Ile Thr
1105				1110						1115				1120
Glu	Met	Gln	Gln	Val	Glu	Ala	Phe	Leu	Arg	Glu	Gly	Leu	Leu	Met Arg
			1125						1130					1135
Gly	Leu	Asn	His	Pro	Asn	Val	Leu	Ala	Leu	Ile	Gly	Ile	Met	Leu Pro
	1140						1145						1150	
Pro	Glu	Gly	Leu	Pro	His	Val	Leu	Leu	Pro	Tyr	Met	Cys	His	Gly Asp
	1155						1160					1165		
Leu	Leu	Gln	Phe	Ile	Arg	Ser	Pro	Gln	Arg	Asn	Pro	Thr	Val	Lys Asp
	1170				1175					1180				
Leu	Ile	Ser	Phe	Gly	Leu	Gln	Val	Ala	Arg	Gly	Met	Glu	Tyr	Leu Ala
1185				1190					1195					1200
Glu	Gln	Lys	Phe	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Cys	Met Leu
			1205						1210					1215
Asp	Glu	Ser	Phe	Thr	Val	Lys	Val	Ala	Asp	Phe	Gly	Leu	Ala	Arg Asp
			1220					1225						1230
Ile	Leu	Asp	Arg	Glu	Tyr	Tyr	Ser	Val	Gln	Gln	His	Arg	His	Ala Arg
	1235						1240					1245		
Leu	Pro	Val	Lys	Trp	Met	Ala	Leu	Glu	Ser	Leu	Gln	Thr	Tyr	Arg Phe
	1250					1255					1260			
Thr	Thr	Lys	Ser	Asp	Val	Trp	Ser	Phe	Gly	Val	Leu	Leu	Trp	Glu Leu
1265				1270					1275					1280
Leu	Thr	Arg	Gly	Ala	Pro	Pro	Tyr	Arg	His	Ile	Asp	Pro	Phe	Asp Leu
			1285						1290					1295
Thr	His	Phe	Leu	Ala	Gln	Gly	Arg	Arg	Leu	Pro	Gln	Pro	Glu	Tyr Cys
	1300						1305						1310	
Pro	Asp	Ser	Leu	Tyr	Gln	Val	Met	Gln	Gln	Cys	Trp	Glu	Ala	Asp Pro



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      1315      1320      1325
Ala Val Arg Pro Thr Phe Arg Val Leu Val Gly Glu Val Glu Gln Ile
      1330      1335      1340
Val Ser Ala Leu Leu Gly Asp His Tyr Val Gln Leu Pro Ala Thr Tyr
1345      1350      1355      1360
Met Asn Leu Gly Pro Ser Thr Ser His Glu Met Asn Val Arg Pro Glu
      1365      1370      1375
Gln Pro Gln Phe Ser Pro Met Pro Gly Asn Val Arg Arg Pro Arg Pro
      1380      1385      1390
Leu Ser Glu Pro Pro Arg Pro Thr
      1395      1400

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<210> 278  
 <211> 1124  
 <212> PRT  
 <213> Homo sapiens

<300>  
 <308> GenBank No. NP000450  
 <309> 2004-10-26

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<400> 278
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Pro Leu Val Ser Asp Ala Glu Thr Ser Leu Thr Cys Ile Ala Ser Gly
      35      40      45
Trp Arg Pro His Glu Pro Ile Thr Ile Gly Arg Asp Phe Glu Ala Leu
      50      55      60
Met Asn Gln His Gln Asp Pro Leu Glu Val Thr Gln Asp Val Thr Arg
      65      70      75      80
Glu Trp Ala Lys Lys Val Val Trp Lys Arg Glu Lys Ala Ser Lys Ile
      85      90      95
Asn Gly Ala Tyr Phe Cys Glu Gly Arg Val Arg Gly Glu Ala Ile Arg
      100      105      110
Ile Arg Thr Met Lys Met Arg Gln Gln Ala Ser Phe Leu Pro Ala Thr
      115      120      125
Leu Thr Met Thr Val Asp Lys Gly Asp Asn Val Asn Ile Ser Phe Lys
      130      135      140
Lys Val Leu Ile Lys Glu Glu Asp Ala Val Ile Tyr Lys Asn Gly Ser
      145      150      155      160
Phe Ile His Ser Val Pro Arg His Glu Val Pro Asp Ile Leu Glu Val
      165      170      175
His Leu Pro His Ala Gln Pro Gln Asp Ala Gly Val Tyr Ser Ala Arg
      180      185      190
Tyr Ile Gly Gly Asn Leu Phe Thr Ser Ala Phe Thr Arg Leu Ile Val
      195      200      205
Arg Arg Cys Glu Ala Gln Lys Trp Gly Pro Glu Cys Asn His Leu Cys
      210      215      220
Thr Ala Cys Met Asn Asn Gly Val Cys His Glu Asp Thr Gly Glu Cys
      225      230      235      240
Ile Cys Pro Pro Gly Phe Met Gly Arg Thr Cys Glu Lys Ala Cys Glu
      245      250      255
Leu His Thr Phe Gly Arg Thr Cys Lys Glu Arg Cys Ser Gly Gln Glu

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			260					265					270				
Gly	Cys	Lys	Ser	Tyr	Val	Phe	Cys	Leu	Pro	Asp	Pro	Tyr	Gly	Cys	Ser		
		275					280					285					
Cys	Ala	Thr	Gly	Trp	Lys	Gly	Leu	Gln	Cys	Asn	Glu	Ala	Cys	His	Pro		
	290					295					300						
Gly	Phe	Tyr	Gly	Pro	Asp	Cys	Lys	Leu	Arg	Cys	Ser	Cys	Asn	Asn	Gly		
305					310					315					320		
Glu	Met	Cys	Asp	Arg	Phe	Gln	Gly	Cys	Leu	Cys	Ser	Pro	Gly	Trp	Gln		
			325						330					335			
Gly	Leu	Gln	Cys	Glu	Arg	Glu	Gly	Ile	Pro	Arg	Met	Thr	Pro	Lys	Ile		
		340					345						350				
Val	Asp	Leu	Pro	Asp	His	Ile	Glu	Val	Asn	Ser	Gly	Lys	Phe	Asn	Pro		
	355						360					365					
Ile	Cys	Lys	Ala	Ser	Gly	Trp	Pro	Leu	Pro	Thr	Asn	Glu	Glu	Met	Thr		
370						375				380							
Leu	Val	Lys	Pro	Asp	Gly	Thr	Val	Leu	His	Pro	Lys	Asp	Phe	Asn	His		
385					390					395					400		
Thr	Asp	His	Phe	Ser	Val	Ala	Ile	Phe	Thr	Ile	His	Arg	Ile	Leu	Pro		
			405						410					415			
Pro	Asp	Ser	Gly	Val	Trp	Val	Cys	Ser	Val	Asn	Thr	Val	Ala	Gly	Met		
		420					425						430				
Val	Glu	Lys	Pro	Phe	Asn	Ile	Ser	Val	Lys	Val	Leu	Pro	Lys	Pro	Leu		
	435						440					445					
Asn	Ala	Pro	Asn	Val	Ile	Asp	Thr	Gly	His	Asn	Phe	Ala	Val	Ile	Asn		
450						455				460							
Ile	Ser	Ser	Glu	Pro	Tyr	Phe	Gly	Asp	Gly	Pro	Ile	Lys	Ser	Lys	Lys		
465					470					475					480		
Leu	Leu	Tyr	Lys	Pro	Val	Asn	His	Tyr	Glu	Ala	Trp	Gln	His	Ile	Gln		
			485						490					495			
Val	Thr	Asn	Glu	Ile	Val	Thr	Leu	Asn	Tyr	Leu	Glu	Pro	Arg	Thr	Glu		
		500					505						510				
Tyr	Glu	Leu	Cys	Val	Gln	Leu	Val	Arg	Arg	Gly	Glu	Gly	Gly	Glu	Gly		
	515						520					525					
His	Pro	Gly	Pro	Val	Arg	Arg	Phe	Thr	Thr	Ala	Ser	Ile	Gly	Leu	Pro		
530						535				540							
Pro	Pro	Arg	Gly	Leu	Asn	Leu	Leu	Pro	Lys	Ser	Gln	Thr	Thr	Leu	Asn		
545					550					555					560		
Leu	Thr	Trp	Gln	Pro	Ile	Phe	Pro	Ser	Ser	Glu	Asp	Asp	Phe	Tyr	Val		
			565						570					575			
Glu	Val	Glu	Arg	Arg	Ser	Val	Gln	Lys	Ser	Asp	Gln	Gln	Asn	Ile	Lys		
		580					585						590				
Val	Pro	Gly	Asn	Leu	Thr	Ser	Val	Leu	Leu	Asn	Asn	Leu	His	Pro	Arg		
	595						600					605					
Glu	Gln	Tyr	Val	Val	Arg	Ala	Arg	Val	Asn	Thr	Lys	Ala	Gln	Gly	Glu		
	610					615					620						
Trp	Ser	Glu	Asp	Leu	Thr	Ala	Trp	Thr	Leu	Ser	Asp	Ile	Leu	Pro	Pro		
625					630				635						640		
Gln	Pro	Glu	Asn	Ile	Lys	Ile	Ser	Asn	Ile	Thr	His	Ser	Ser	Ala	Val		
			645						650					655			
Ile	Ser	Trp	Thr	Ile	Leu	Asp	Gly	Tyr	Ser	Ile	Ser	Ser	Ile	Thr	Ile		
		660					665						670				
Arg	Tyr	Lys	Val	Gln	Gly	Lys	Asn	Glu	Asp	Gln	His	Val	Asp	Val	Lys		
	675						680					685					
Ile	Lys	Asn	Ala	Thr	Ile	Ile	Gln	Tyr	Gln	Leu	Lys	Gly	Leu	Glu	Pro		
	690					695				700							
Glu	Thr	Ala	Tyr	Gln	Val	Asp	Ile	Phe	Ala	Glu	Asn	Asn	Ile	Gly	Ser		

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705					710					715				720
Ser	Asn	Pro	Ala	Phe	Ser	His	Glu	Leu	Val	Thr	Leu	Pro	Glu	Ser
				725					730				735	
Ala	Pro	Ala	Asp	Leu	Gly	Gly	Gly	Lys	Met	Leu	Leu	Ile	Ala	Ile
			740					745					750	
Gly	Ser	Ala	Gly	Met	Thr	Cys	Leu	Thr	Val	Leu	Leu	Ala	Phe	Leu
		755					760					765		
Ile	Leu	Gln	Leu	Lys	Arg	Ala	Asn	Val	Gln	Arg	Arg	Met	Ala	Gln
	770					775					780			
Phe	Gln	Asn	Val	Arg	Glu	Glu	Pro	Ala	Val	Gln	Phe	Asn	Ser	Gly
785					790				795					800
Leu	Ala	Leu	Asn	Arg	Lys	Val	Lys	Asn	Asn	Pro	Asp	Pro	Thr	Ile
			805						810					815
Pro	Val	Leu	Asp	Trp	Asn	Asp	Ile	Lys	Phe	Gln	Asp	Val	Ile	Gly
			820					825					830	
Gly	Asn	Phe	Gly	Gln	Val	Leu	Lys	Ala	Arg	Ile	Lys	Lys	Asp	Gly
	835						840					845		
Arg	Met	Asp	Ala	Ala	Ile	Lys	Arg	Met	Lys	Glu	Tyr	Ala	Ser	Lys
	850					855					860			
Asp	His	Arg	Asp	Phe	Ala	Gly	Glu	Leu	Glu	Val	Leu	Cys	Lys	Leu
865					870					875				880
His	His	Pro	Asn	Ile	Asn	Leu	Leu	Gly	Ala	Cys	Glu	His	Arg	Gly
			885					890					895	
Tyr	Leu	Tyr	Leu	Ala	Ile	Glu	Tyr	Ala	Pro	His	Gly	Asn	Leu	Leu
		900						905					910	
Phe	Leu	Arg	Lys	Ser	Arg	Val	Leu	Glu	Thr	Asp	Pro	Ala	Phe	Ala
		915						920					925	
Ala	Asn	Ser	Thr	Ala	Ser	Thr	Leu	Ser	Ser	Gln	Gln	Leu	Leu	His
	930					935					940			
Ala	Ala	Asp	Val	Ala	Arg	Gly	Met	Asp	Tyr	Leu	Ser	Gln	Lys	Gln
945					950					955				960
Ile	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Val	Gly	Glu	Asn
			965						970					975
Val	Ala	Lys	Ile	Ala	Asp	Phe	Gly	Leu	Ser	Arg	Gly	Gln	Glu	Val
			980					985					990	
Val	Lys	Lys	Thr	Met	Gly	Arg	Leu	Pro	Val	Arg	Trp	Met	Ala	Ile
		995					1000					1005		
Ser	Leu	Asn	Tyr	Ser	Val	Tyr	Thr	Thr	Asn	Ser	Asp	Val	Trp	Ser
	1010					1015					1020			
Gly	Val	Leu	Leu	Trp	Glu	Ile	Val	Ser	Leu	Gly	Gly	Thr	Pro	Tyr
1025					1030					1035				1040
Gly	Met	Thr	Cys	Ala	Glu	Leu	Tyr	Glu	Lys	Leu	Pro	Gln	Gly	Tyr
			1045						1050					1055
Leu	Glu	Lys	Pro	Leu	Asn	Cys	Asp	Asp	Glu	Val	Tyr	Asp	Leu	Met
			1060					1065					1070	
Gln	Cys	Trp	Arg	Glu	Lys	Pro	Tyr	Glu	Arg	Pro	Ser	Phe	Ala	Gln
		1075					1080					1085		
Leu	Val	Ser	Leu	Asn	Arg	Met	Leu	Glu	Glu	Arg	Lys	Thr	Tyr	Val
	1090					1095					1100			
Thr	Thr	Leu	Tyr	Glu	Lys	Phe	Thr	Tyr	Ala	Gly	Ile	Asp	Cys	Ser
1105					1110					1115				1120
Glu	Glu	Ala	Ala											

&lt;210&gt; 279

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&lt;211&gt; 1138

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank No. NP005415

&lt;309&gt; 2004-12-18

&lt;400&gt; 279

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Met Val Trp Arg Val Pro Pro Phe Leu Leu Pro Ile Leu Phe Leu Ala
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      20           25           30
Leu Thr Asp Pro Gln Arg Phe Phe Leu Thr Cys Val Ser Gly Glu Ala
      35           40           45
Gly Ala Gly Arg Gly Ser Asp Ala Trp Gly Pro Pro Leu Leu Leu Glu
 50           55           60
Lys Asp Asp Arg Ile Val Arg Thr Pro Pro Gly Pro Pro Leu Arg Leu
 65           70           75           80
Ala Arg Asn Gly Ser His Gln Val Thr Leu Arg Gly Phe Ser Lys Pro
      85           90           95
Ser Asp Leu Val Gly Val Phe Ser Cys Val Gly Gly Ala Gly Ala Arg
      100           105           110
Arg Thr Arg Val Ile Tyr Val His Asn Ser Pro Gly Ala His Leu Leu
      115           120           125
Pro Asp Lys Val Thr His Thr Val Asn Lys Gly Asp Thr Ala Val Leu
      130           135           140
Ser Ala Arg Val His Lys Glu Lys Gln Thr Asp Val Ile Trp Lys Ser
 145           150           155           160
Asn Gly Ser Tyr Phe Tyr Thr Leu Asp Trp His Glu Ala Gln Asp Gly
      165           170           175
Arg Phe Leu Leu Gln Leu Pro Asn Val Gln Pro Pro Ser Ser Gly Ile
      180           185           190
Tyr Ser Ala Thr Tyr Leu Glu Ala Ser Pro Leu Gly Ser Ala Phe Phe
      195           200           205
Arg Leu Ile Val Arg Gly Cys Gly Ala Gly Arg Trp Gly Pro Gly Cys
 210           215           220
Thr Lys Glu Cys Pro Gly Cys Leu His Gly Gly Val Cys His Asp His
 225           230           235           240
Asp Gly Glu Cys Val Cys Pro Pro Gly Phe Thr Gly Thr Arg Cys Glu
      245           250           255
Gln Ala Cys Arg Glu Gly Arg Phe Gly Gln Ser Cys Gln Glu Gln Cys
      260           265           270
Pro Gly Ile Ser Gly Cys Arg Gly Leu Thr Phe Cys Leu Pro Asp Pro
      275           280           285
Tyr Gly Cys Ser Cys Gly Ser Gly Trp Arg Gly Ser Gln Cys Gln Glu
 290           295           300
Ala Cys Ala Pro Gly His Phe Gly Ala Asp Cys Arg Leu Gln Cys Gln
 305           310           315           320
Cys Gln Asn Gly Gly Thr Cys Asp Arg Phe Ser Gly Cys Val Cys Pro
      325           330           335
Ser Gly Trp His Gly Val His Cys Glu Lys Ser Asp Arg Ile Pro Gln
      340           345           350
Ile Leu Asn Met Ala Ser Glu Leu Glu Phe Asn Leu Glu Thr Met Pro
      355           360           365
Arg Ile Asn Cys Ala Ala Ala Gly Asn Pro Phe Pro Val Arg Gly Ser

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370		375		380
Ile Glu Leu Arg Lys Pro Asp Gly Thr Val Leu Leu Ser Thr Lys Ala				
385		390		395
Ile Val Glu Pro Glu Lys Thr Thr Ala Glu Phe Glu Val Pro Arg Leu				
	405		410	415
Val Leu Ala Asp Ser Gly Phe Trp Glu Cys Arg Val Ser Thr Ser Gly				
	420		425	430
Gly Gln Asp Ser Arg Arg Phe Lys Val Asn Val Lys Val Pro Pro Val				
	435		440	445
Pro Leu Ala Ala Pro Arg Leu Leu Thr Lys Gln Ser Arg Gln Leu Val				
	450		455	460
Val Ser Pro Leu Val Ser Phe Ser Gly Asp Gly Pro Ile Ser Thr Val				
465		470		475
Arg Leu His Tyr Arg Pro Gln Asp Ser Thr Met Asp Trp Ser Thr Ile				
	485		490	495
Val Val Asp Pro Ser Glu Asn Val Thr Leu Met Asn Leu Arg Pro Lys				
	500		505	510
Thr Gly Tyr Ser Val Arg Val Gln Leu Ser Arg Pro Gly Glu Gly Gly				
	515		520	525
Glu Gly Ala Trp Gly Pro Pro Thr Leu Met Thr Thr Asp Cys Pro Glu				
	530		535	540
Pro Leu Leu Gln Pro Trp Leu Glu Gly Trp His Val Glu Gly Thr Asp				
545		550		555
Arg Leu Arg Val Ser Trp Ser Leu Pro Leu Val Pro Gly Pro Leu Val				
	565		570	575
Gly Asp Gly Phe Leu Leu Arg Leu Trp Asp Gly Thr Arg Gly Gln Glu				
	580		585	590
Arg Arg Glu Asn Val Ser Ser Pro Gln Ala Arg Thr Ala Leu Leu Thr				
	595		600	605
Gly Leu Thr Pro Gly Thr His Tyr Gln Leu Asp Val Gln Leu Tyr His				
	610		615	620
Cys Thr Leu Leu Gly Pro Ala Ser Pro Pro Ala His Val Leu Leu Pro				
625		630		635
Pro Ser Gly Pro Pro Ala Pro Arg His Leu His Ala Gln Ala Leu Ser				
	645		650	655
Asp Ser Glu Ile Gln Leu Thr Trp Lys His Pro Glu Ala Leu Pro Gly				
	660		665	670
Pro Ile Ser Lys Tyr Val Val Glu Val Gln Val Ala Gly Gly Ala Gly				
	675		680	685
Asp Pro Leu Trp Ile Asp Val Asp Arg Pro Glu Glu Thr Ser Thr Ile				
	690		695	700
Ile Arg Gly Leu Asn Ala Ser Thr Arg Tyr Leu Phe Arg Met Arg Ala				
705		710		715
Ser Ile Gln Gly Leu Gly Asp Trp Ser Asn Thr Val Glu Glu Ser Thr				
	725		730	735
Leu Gly Asn Gly Leu Gln Ala Glu Gly Pro Val Gln Glu Ser Arg Ala				
	740		745	750
Ala Glu Glu Gly Leu Asp Gln Gln Leu Ile Leu Ala Val Val Gly Ser				
	755		760	765
Val Ser Ala Thr Cys Leu Thr Ile Leu Ala Ala Leu Leu Thr Leu Val				
	770		775	780
Cys Ile Arg Arg Ser Cys Leu His Arg Arg Arg Thr Phe Thr Tyr Gln				
785		790		795
Ser Gly Ser Gly Glu Glu Thr Ile Leu Gln Phe Ser Ser Gly Thr Leu				
	805		810	815
Thr Leu Thr Arg Arg Pro Lys Leu Gln Pro Glu Pro Leu Ser Tyr Pro				

				820					825					830			
Val	Leu	Glu	Trp	Glu	Asp	Ile	Thr	Phe	Glu	Asp	Leu	Ile	Gly	Glu	Gly		
		835					840					845					
Asn	Phe	Gly	Gln	Val	Ile	Arg	Ala	Met	Ile	Lys	Lys	Asp	Gly	Leu	Lys		
		850				855						860					
Met	Asn	Ala	Ala	Ile	Lys	Met	Leu	Lys	Glu	Tyr	Ala	Ser	Glu	Asn	Asp		
865					870					875					880		
His	Arg	Asp	Phe	Ala	Gly	Glu	Leu	Glu	Val	Leu	Cys	Lys	Leu	Gly	His		
				885					890					895			
His	Pro	Asn	Ile	Ile	Asn	Leu	Leu	Gly	Ala	Cys	Lys	Asn	Arg	Gly	Tyr		
			900					905					910				
Leu	Tyr	Ile	Ala	Ile	Glu	Tyr	Ala	Pro	Tyr	Gly	Asn	Leu	Leu	Asp	Phe		
		915					920					925					
Leu	Arg	Lys	Ser	Arg	Val	Leu	Glu	Thr	Asp	Pro	Ala	Phe	Ala	Arg	Glu		
		930				935					940						
His	Gly	Thr	Ala	Ser	Thr	Leu	Ser	Ser	Arg	Gln	Leu	Leu	Arg	Phe	Ala		
945					950					955					960		
Ser	Asp	Ala	Ala	Asn	Gly	Met	Gln	Tyr	Leu	Ser	Glu	Lys	Gln	Phe	Ile		
				965					970					975			
His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Val	Leu	Val	Gly	Glu	Asn	Leu	Ala		
			980					985					990				
Ser	Lys	Ile	Ala	Asp	Phe	Gly	Leu	Ser	Arg	Gly	Glu	Glu	Val	Tyr	Val		
		995				1000						1005					
Lys	Lys	Thr	Met	Gly	Arg	Leu	Pro	Val	Arg	Trp	Met	Ala	Ile	Glu	Ser		
		1010				1015					1020						
Leu	Asn	Tyr	Ser	Val	Tyr	Thr	Thr	Lys	Ser	Asp	Val	Trp	Ser	Phe	Gly		
1025					1030					1035					1040		
Val	Leu	Leu	Trp	Glu	Ile	Val	Ser	Leu	Gly	Gly	Thr	Pro	Tyr	Cys	Gly		
				1045					1050					1055			
Met	Thr	Cys	Ala	Glu	Leu	Tyr	Glu	Lys	Leu	Pro	Gln	Gly	Tyr	Arg	Met		
			1060					1065					1070				
Glu	Gln	Pro	Arg	Asn	Cys	Asp	Asp	Glu	Val	Tyr	Glu	Leu	Met	Arg	Gln		
		1075					1080					1085					
Cys	Trp	Arg	Asp	Arg	Pro	Tyr	Glu	Arg	Pro	Pro	Phe	Ala	Gln	Ile	Ala		
		1090				1095					1100						
Leu	Gln	Leu	Gly	Arg	Met	Leu	Glu	Ala	Arg	Lys	Ala	Tyr	Val	Asn	Met		
1105					1110					1115					1120		
Ser	Leu	Phe	Glu	Asn	Phe	Thr	Tyr	Ala	Gly	Ile	Asp	Ala	Thr	Ala	Glu		
				1125					1130					1135			

<300>  
<308> GenBank No. NP001056  
<309> 2004-10-27

<400> 280  
Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu  
1 5 10 15  
Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro

			20					25					30			
His	Leu	Gly	Asp	Arg	Glu	Lys	Arg	Asp	Ser	Val	Cys	Pro	Gln	Gly	Lys	
		35					40					45				
Tyr	Ile	His	Pro	Gln	Asn	Asn	Ser	Ile	Cys	Cys	Thr	Lys	Cys	His	Lys	
	50					55					60					
Gly	Thr	Tyr	Leu	Tyr	Asn	Asp	Cys	Pro	Gly	Pro	Gly	Gln	Asp	Thr	Asp	
65					70					75					80	
Cys	Arg	Glu	Cys	Glu	Ser	Gly	Ser	Phe	Thr	Ala	Ser	Glu	Asn	His	Leu	
				85					90					95		
Arg	His	Cys	Leu	Ser	Cys	Ser	Lys	Cys	Arg	Lys	Glu	Met	Gly	Gln	Val	
			100					105					110			
Glu	Ile	Ser	Ser	Cys	Thr	Val	Asp	Arg	Asp	Thr	Val	Cys	Gly	Cys	Arg	
		115					120					125				
Lys	Asn	Gln	Tyr	Arg	His	Tyr	Trp	Ser	Glu	Asn	Leu	Phe	Gln	Cys	Phe	
	130					135					140					
Asn	Cys	Ser	Leu	Cys	Leu	Asn	Gly	Thr	Val	His	Leu	Ser	Cys	Gln	Glu	
145					150					155					160	
Lys	Gln	Asn	Thr	Val	Cys	Thr	Cys	His	Ala	Gly	Phe	Phe	Leu	Arg	Glu	
				165					170					175		
Asn	Glu	Cys	Val	Ser	Cys	Ser	Asn	Cys	Lys	Lys	Ser	Leu	Glu	Cys	Thr	
			180					185					190			
Lys	Leu	Cys	Leu	Pro	Gln	Ile	Glu	Asn	Val	Lys	Gly	Thr	Glu	Asp	Ser	
		195					200					205				
Gly	Thr	Thr	Val	Leu	Leu	Pro	Leu	Val	Ile	Phe	Phe	Gly	Leu	Cys	Leu	
	210					215					220					
Leu	Ser	Leu	Leu	Phe	Ile	Gly	Leu	Met	Tyr	Arg	Tyr	Gln	Arg	Trp	Lys	
225					230					235					240	
Ser	Lys	Leu	Tyr	Ser	Ile	Val	Cys	Gly	Lys	Ser	Thr	Pro	Glu	Lys	Glu	
				245					250					255		
Gly	Glu	Leu	Glu	Gly	Thr	Thr	Thr	Lys	Pro	Leu	Ala	Pro	Asn	Pro	Ser	
			260					265					270			
Phe	Ser	Pro	Thr	Pro	Gly	Phe	Thr	Pro	Thr	Leu	Gly	Phe	Ser	Pro	Val	
		275					280					285				
Pro	Ser	Ser	Thr	Phe	Thr	Ser	Ser	Ser	Thr	Tyr	Thr	Pro	Gly	Asp	Cys	
	290					295					300					
Pro	Asn	Phe	Ala	Ala	Pro	Arg	Arg	Glu	Val	Ala	Pro	Pro	Tyr	Gln	Gly	
305					310					315					320	
Ala	Asp	Pro	Ile	Leu	Ala	Thr	Ala	Leu	Ala	Ser	Asp	Pro	Ile	Pro	Asn	
				325					330					335		
Pro	Leu	Gln	Lys	Trp	Glu	Asp	Ser	Ala	His	Lys	Pro	Gln	Ser	Leu	Asp	
			340					345					350			
Thr	Asp</															

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<210> 281  
 <211> 461  
 <212> PRT  
 <213> Homo sapiens

<300>  
 <308> GenBank No. NP001057  
 <309> 2004-10-26

<400> 281  
 Met Ala Pro Val Ala Val Trp Ala Ala Leu Ala Val Gly Leu Glu Leu  
 1 5 10 15  
 Trp Ala Ala Ala His Ala Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr  
 20 25 30  
 Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Asp Gln  
 35 40 45  
 Thr Ala Gln Met Cys Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys  
 50 55 60  
 Val Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp  
 65 70 75 80  
 Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu Ser Cys  
 85 90 95  
 Gly Ser Arg Cys Ser Ser Asp Gln Val Glu Thr Gln Ala Cys Thr Arg  
 100 105 110  
 Glu Gln Asn Arg Ile Cys Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu  
 115 120 125  
 Ser Lys Gln Glu Gly Cys Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg  
 130 135 140  
 Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Asp Val Val  
 145 150 155 160  
 Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr  
 165 170 175  
 Asp Ile Cys Arg Pro His Gln Ile Cys Asn Val Val Ala Ile Pro Gly  
 180 185 190  
 Asn Ala Ser Met Asp Ala Val Cys Thr Ser Thr Ser Pro Thr Arg Ser  
 195 200 205  
 Met Ala Pro Gly Ala Val His Leu Pro Gln Pro Val Ser Thr Arg Ser  
 210 215 220  
 Gln His Thr Gln Pro Thr Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser  
 225 230 235 240  
 Phe Leu Leu Pro Met Gly Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly  
 245 250 255  
 Asp Phe Ala Leu Pro Val Gly Leu Ile Val Gly Val Thr Ala Leu Gly  
 260 265 270  
 Leu Leu Ile Ile Gly Val Val Asn Cys Val Ile Met Thr Gln Val Lys  
 275 280 285  
 Lys Lys Pro Leu Cys Leu Gln Arg Glu Ala Lys Val Pro His Leu Pro  
 290 295 300  
 Ala Asp Lys Ala Arg Gly Thr Gln Gly Pro Glu Gln Gln His Leu Leu  
 305 310 315 320  
 Ile Thr Ala Pro Ser Ser Ser Ser Ser Leu Glu Ser Ser Ala Ser  
 325 330 335  
 Ala Leu Asp Arg Arg Ala Pro Thr Arg Asn Gln Pro Gln Ala Pro Gly  
 340 345 350  
 Val Glu Ala Ser Gly Ala Gly Glu Ala Arg Ala Ser Thr Gly Ser Ser



Asp	Ser	Ser	Pro	Gly	Gly	His	Gly	Thr	Gln	Val	Asn	Val	Thr	Cys	Ile
Val	Asn	Val	Cys	Ser	Ser	Ser	Asp	His	Ser	Ser	Gln	Cys	Ser	Ser	Gln
Ala	Ser	Ser	Thr	Met	Gly	Asp	Thr	Asp	Ser	Ser	Pro	Ser	Glu	Ser	Pro
Lys	Asp	Glu	Gln	Val	Pro	Phe	Ser	Lys	Glu	Glu	Cys	Ala	Phe	Arg	Ser
Gln	Leu	Glu	Thr	Pro	Glu	Thr	Leu	Leu	Gly	Ser	Thr	Glu	Glu	Lys	Pro
Leu	Pro	Leu	Gly	Val	Pro	Asp	Ala	Gly	Met	Lys	Pro	Ser			

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<210> 282
<211> 1338
<212> PRT
<213> Homo sapiens
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<300>  
<308> GenBank No. NP002010  
<309> 2004-10-28

<400>	282																
Met	Val	Ser	Tyr	Trp	Asp	Thr	Gly	Val	Leu	Leu	Cys	Ala	Leu	Leu	Ser		
1				5					10					15			
Cys	Leu	Leu	Leu	Thr	Gly	Ser	Ser	Ser	Gly	Ser	Lys	Leu	Lys	Asp	Pro		
			20					25					30				
Glu	Leu	Ser	Leu	Lys	Gly	Thr	Gln	His	Ile	Met	Gln	Ala	Gly	Gln	Thr		
	35						40					45					
Leu	His	Leu	Gln	Cys	Arg	Gly	Glu	Ala	Ala	His	Lys	Trp	Ser	Leu	Pro		
	50					55					60						
Glu	Met	Val	Ser	Lys	Glu	Ser	Glu	Arg	Leu	Ser	Ile	Thr	Lys	Ser	Ala		
65				70						75					80		
Cys	Gly	Arg	Asn	Gly	Lys	Gln	Phe	Cys	Ser	Thr	Leu	Thr	Leu	Asn	Thr		
			85						90					95			
Ala	Gln	Ala	Asn	His	Thr	Gly	Phe	Tyr	Ser	Cys	Lys	Tyr	Leu	Ala	Val		
			100					105					110				
Pro	Thr	Ser	Lys	Lys	Lys	Glu	Thr	Glu	Ser	Ala	Ile	Tyr	Ile	Phe	Ile		
		115					120					125					
Ser	Asp	Thr	Gly	Arg	Pro	Phe	Val	Glu	Met	Tyr	Ser	Glu	Ile	Pro	Glu		
	130					135					140						
Ile	Ile	His	Met	Thr	Glu	Gly	Arg	Glu	Leu	Val	Ile	Pro	Cys	Arg	Val		
145				150					155					160			
Thr	Ser	Pro	Asn	Ile	Thr	Val	Thr	Leu	Lys	Lys	Phe	Pro	Leu	Asp	Thr		
			165						170					175			
Leu	Ile	Pro	Asp	Gly	Lys	Arg	Ile	Ile	Trp	Asp	Ser	Arg	Lys	Gly	Phe		
			180					185					190				
Ile	Ile	Ser	Asn	Ala	Thr	Tyr	Lys	Glu	Ile	Gly	Leu	Leu	Thr	Cys	Glu		
	195						200				205						
Ala	Thr	Val	Asn	Gly	His	Leu	Tyr	Lys	Thr	Asn	Tyr	Leu	Thr	His	Arg		
	210					215				220							
Gln	Thr	Asn	Thr	Ile	Ile	Asp	Val	Gln	Ile	Ser	Thr	Pro	Arg	Pro	Val		
225				230						235				240			
Lys	Leu	Leu	Arg	Gly	His	Thr	Leu	Val	Leu	Asn	Cys	Thr	Ala	Thr	Thr		

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				245				250					255				
Pro	Leu	Asn	Thr	Arg	Val	Gln	Met	Thr	Trp	Ser	Tyr	Pro	Asp	Glu	Lys		
			260					265					270				
Asn	Lys	Arg	Ala	Ser	Val	Arg	Arg	Arg	Ile	Asp	Gln	Ser	Asn	Ser	His		
		275					280					285					
Ala	Asn	Ile	Phe	Tyr	Ser	Val	Leu	Thr	Ile	Asp	Lys	Met	Gln	Asn	Lys		
	290					295					300						
Asp	Lys	Gly	Leu	Tyr	Thr	Cys	Arg	Val	Arg	Ser	Gly	Pro	Ser	Phe	Lys		
305					310					315					320		
Ser	Val	Asn	Thr	Ser	Val	His	Ile	Tyr	Asp	Lys	Ala	Phe	Ile	Thr	Val		
			325						330					335			
Lys	His	Arg	Lys	Gln	Gln	Val	Leu	Glu	Thr	Val	Ala	Gly	Lys	Arg	Ser		
		340						345					350				
Tyr	Arg	Leu	Ser	Met	Lys	Val	Lys	Ala	Phe	Pro	Ser	Pro	Glu	Val	Val		
	355					360						365					
Trp	Leu	Lys	Asp	Gly	Leu	Pro	Ala	Thr	Glu	Lys	Ser	Ala	Arg	Tyr	Leu		
	370					375					380						
Thr	Arg	Gly	Tyr	Ser	Leu	Ile	Ile	Lys	Asp	Val	Thr	Glu	Glu	Asp	Ala		
385					390					395					400		
Gly	Asn	Tyr	Thr	Ile	Leu	Leu	Ser	Ile	Lys	Gln	Ser	Asn	Val	Phe	Lys		
			405						410					415			
Asn	Leu	Thr	Ala	Thr	Leu	Ile	Val	Asn	Val	Lys	Pro	Gln	Ile	Tyr	Glu		
		420						425					430				
Lys	Ala	Val	Ser	Ser	Phe	Pro	Asp	Pro	Ala	Leu	Tyr	Pro	Leu	Gly	Ser		
	435						440					445					
Arg	Gln	Ile	Leu	Thr	Cys	Thr	Ala	Tyr	Gly	Ile	Pro	Gln	Pro	Thr	Ile		
	450					455					460						
Lys	Trp	Phe	Trp	His	Pro	Cys	Asn	His	Asn	His	Ser	Glu	Ala	Arg	Cys		
465					470					475					480		
Asp	Phe	Cys	Ser	Asn	Asn	Glu	Glu	Ser	Phe	Ile	Leu	Asp	Ala	Asp	Ser		
			485						490					495			
Asn	Met	Gly	Asn	Arg	Ile	Glu	Ser	Ile	Thr	Gln	Arg	Met	Ala	Ile	Ile		
		500						505					510				
Glu	Gly	Lys	Asn	Lys	Met	Ala	Ser	Thr	Leu	Val	Val	Ala	Asp	Ser	Arg		
	515							520					525				
Ile	Ser	Gly	Ile	Tyr	Ile	Cys	Ile	Ala	Ser	Asn	Lys	Val	Gly	Thr	Val		
	530					535					540						
Gly	Arg	Asn	Ile	Ser	Phe	Tyr	Ile	Thr	Asp	Val	Pro	Asn	Gly	Phe	His		
545					550					555					560		
Val	Asn	Leu	Glu	Lys	Met	Pro	Thr	Glu	Gly	Glu	Asp	Leu	Lys	Leu	Ser		
			565						570					575			
Cys	Thr	Val	Asn	Lys	Phe	Leu	Tyr	Arg	Asp	Val	Thr	Trp	Ile	Leu	Leu		
		580						585					590				
Arg	Thr	Val	Asn	Asn	Arg	Thr	Met	His	Tyr	Ser	Ile	Ser	Lys	Gln	Lys		
		595					600					605					
Met	Ala	Ile	Thr	Lys	Glu	His	Ser	Ile	Thr	Leu	Asn	Leu	Thr	Ile	Met		
	610					615						620					
Asn	Val	Ser	Leu	Gln	Asp	Ser	Gly	Thr	Tyr	Ala	Cys	Arg	Ala	Arg	Asn		
625					630					635					640		
Val	Tyr	Thr	Gly	Glu	Glu	Ile	Leu	Gln	Lys	Lys	Glu	Ile	Thr	Ile	Arg		
			645						650					655			
Asp	Gln	Glu	Ala	Pro	Tyr	Leu	Leu	Arg	Asn	Leu	Ser	Asp	His	Thr	Val		
		660						665					670				
Ala	Ile	Ser	Ser	Ser	Thr	Thr	Leu	Asp	Cys	His	Ala	Asn	Gly	Val	Pro		
		675					680					685					
Glu	Pro	Gln	Ile	Thr	Trp	Phe	Lys	Asn	Asn	His	Lys	Ile	Gln	Gln	Glu		

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690	695	700
Pro Gly Ile Ile Leu Gly	Pro Gly Ser Ser Thr Leu Phe Ile Glu Arg	
705	710	715
Val Thr Glu Glu Asp Glu Gly Val Tyr His Cys Lys Ala Thr Asn Gln		720
	725	730
Lys Gly Ser Val Glu Ser Ser Ala Tyr Leu Thr Val Gln Gly Thr Ser		735
	740	745
Asp Lys Ser Asn Leu Glu Leu Ile Thr Leu Thr Cys Thr Cys Val Ala		750
	755	760
Ala Thr Leu Phe Trp Leu Leu Leu Thr Leu Leu Ile Arg Lys Met Lys		765
	770	775
Arg Ser Ser Ser Glu Ile Lys Thr Asp Tyr Leu Ser Ile Ile Met Asp		780
785	790	795
Pro Asp Glu Val Pro Leu Asp Glu Gln Cys Glu Arg Leu Pro Tyr Asp		800
	805	810
Ala Ser Lys Trp Glu Phe Ala Arg Glu Arg Leu Lys Leu Gly Lys Ser		815
	820	825
Leu Gly Arg Gly Ala Phe Gly Lys Val Val Gln Ala Ser Ala Phe Gly		830
	835	840
Ile Lys Lys Ser Pro Thr Cys Arg Thr Val Ala Val Lys Met Leu Lys		845
	850	855
Glu Gly Ala Thr Ala Ser Glu Tyr Lys Ala Leu Met Thr Glu Leu Lys		860
865	870	875
Ile Leu Thr His Ile Gly His His Leu Asn Val Val Asn Leu Leu Gly		880
	885	890
Ala Cys Thr Lys Gln Gly Gly Pro Leu Met Val Ile Val Glu Tyr Cys		895
	900	905
Lys Tyr Gly Asn Leu Ser Asn Tyr Leu Lys Ser Lys Arg Asp Leu Phe		910
	915	920
Phe Leu Asn Lys Asp Ala Ala Leu His Met Glu Pro Lys Lys Glu Lys		925
	930	935
Met Glu Pro Gly Leu Glu Gln Gly Lys Lys Pro Arg Leu Asp Ser Val		940
945	950	955
Thr Ser Ser Glu Ser Phe Ala Ser Ser Gly Phe Gln Glu Asp Lys Ser		960
	965	970
Leu Ser Asp Val Glu Glu Glu Glu Asp Ser Asp Gly Phe Tyr Lys Glu		975
	980	985
Pro Ile Thr Met Glu Asp Leu Ile Ser Tyr Ser Phe Gln Val Ala Arg		990
	995	1000
Gly Met Glu Phe Leu Ser Ser Arg Lys Cys Ile His Arg Asp Leu Ala		1005
	1010	1015
Ala Arg Asn Ile Leu Leu Ser Glu Asn Asn Val Val Lys Ile Cys Asp		1020
1025	1030	1035
Phe Gly Leu Ala Arg Asp Ile Tyr Lys Asn Pro Asp Tyr Val Arg Lys		1040
	1045	1050
Gly Asp Thr Arg Leu Pro Leu Lys Trp Met Ala Pro Glu Ser Ile Phe		1055
	1060	1065
Asp Lys Ile Tyr Ser Thr Lys Ser Asp Val Trp Ser Tyr Gly Val Leu		1070
	1075	1080
Leu Trp Glu Ile Phe Ser Leu Gly Gly Ser Pro Tyr Pro Gly Val Gln		1085
	1090	1095
Met Asp Glu Asp Phe Cys Ser Arg Leu Arg Glu Gly Met Arg Met Arg		1100
1105	1110	1115
Ala Pro Glu Tyr Ser Thr Pro Glu Ile Tyr Gln Ile Met Leu Asp Cys		1120
	1125	1130
Trp His Arg Asp Pro Lys Glu Arg Pro Arg Phe Ala Glu Leu Val Glu		1135

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      1140      1145      1150
Lys Leu Gly Asp Leu Leu Gln Ala Asn Val Gln Gln Asp Gly Lys Asp
      1155      1160      1165
Tyr Ile Pro Ile Asn Ala Ile Leu Thr Gly Asn Ser Gly Phe Thr Tyr
      1170      1175      1180
Ser Thr Pro Ala Phe Ser Glu Asp Phe Phe Lys Glu Ser Ile Ser Ala
      1185      1190      1195      1200
Pro Lys Phe Asn Ser Gly Ser Ser Asp Asp Val Arg Tyr Val Asn Ala
      1205      1210      1215
Phe Lys Phe Met Ser Leu Glu Arg Ile Lys Thr Phe Glu Glu Leu Leu
      1220      1225      1230
Pro Asn Ala Thr Ser Met Phe Asp Asp Tyr Gln Gly Asp Ser Ser Thr
      1235      1240      1245
Leu Leu Ala Ser Pro Met Leu Lys Arg Phe Thr Trp Thr Asp Ser Lys
      1250      1255      1260
Pro Lys Ala Ser Leu Lys Ile Asp Leu Arg Val Thr Ser Lys Ser Lys
      1265      1270      1275      1280
Glu Ser Gly Leu Ser Asp Val Ser Arg Pro Ser Phe Cys His Ser Ser
      1285      1290      1295
Cys Gly His Val Ser Glu Gly Lys Arg Arg Phe Thr Tyr Asp His Ala
      1300      1305      1310
Glu Leu Glu Arg Lys Ile Ala Cys Cys Ser Pro Pro Pro Asp Tyr Asn
      1315      1320      1325
Ser Val Val Leu Tyr Ser Thr Pro Pro Ile
      1330      1335

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<210> 283
<211> 1356
<212> PRT
<213> Homo sapiens

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<300>
<308> GenBank No. NP002244
<309> 2004-10-26

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<400> 283
Met Gln Ser Lys Val Leu Leu Ala Val Ala Leu Trp Leu Cys Val Glu
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Thr Arg Ala Ala Ser Val Gly Leu Pro Ser Val Ser Leu Asp Leu Pro
      20      25      30
Arg Leu Ser Ile Gln Lys Asp Ile Leu Thr Ile Lys Ala Asn Thr Thr
      35      40      45
Leu Gln Ile Thr Cys Arg Gly Gln Arg Asp Leu Asp Trp Leu Trp Pro
      50      55      60
Asn Asn Gln Ser Gly Ser Glu Gln Arg Val Glu Val Thr Glu Cys Ser
      65      70      75      80
Asp Gly Leu Phe Cys Lys Thr Leu Thr Ile Pro Lys Val Ile Gly Asn
      85      90      95
Asp Thr Gly Ala Tyr Lys Cys Phe Tyr Arg Glu Thr Asp Leu Ala Ser
      100      105      110
Val Ile Tyr Val Tyr Val Gln Asp Tyr Arg Ser Pro Phe Ile Ala Ser
      115      120      125
Val Ser Asp Gln His Gly Val Val Tyr Ile Thr Glu Asn Lys Asn Lys
      130      135      140
Thr Val Val Ile Pro Cys Leu Gly Ser Ile Ser Asn Leu Asn Val Ser

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145					150					155				160	
Leu	Cys	Ala	Arg	Tyr	Pro	Glu	Lys	Arg	Phe	Val	Pro	Asp	Gly	Asn	Arg
				165					170					175	
Ile	Ser	Trp	Asp	Ser	Lys	Lys	Gly	Phe	Thr	Ile	Pro	Ser	Tyr	Met	Ile
			180					185					190		
Ser	Tyr	Ala	Gly	Met	Val	Phe	Cys	Glu	Ala	Lys	Ile	Asn	Asp	Glu	Ser
		195					200					205			
Tyr	Gln	Ser	Ile	Met	Tyr	Ile	Val	Val	Val	Val	Gly	Tyr	Arg	Ile	Tyr
	210					215					220				
Asp	Val	Val	Leu	Ser	Pro	Ser	His	Gly	Ile	Glu	Leu	Ser	Val	Gly	Glu
225					230					235				240	
Lys	Leu	Val	Leu	Asn	Cys	Thr	Ala	Arg	Thr	Glu	Leu	Asn	Val	Gly	Ile
			245						250					255	
Asp	Phe	Asn	Trp	Glu	Tyr	Pro	Ser	Ser	Lys	His	Gln	His	Lys	Lys	Leu
		260						265					270		
Val	Asn	Arg	Asp	Leu	Lys	Thr	Gln	Ser	Gly	Ser	Glu	Met	Lys	Lys	Phe
	275						280					285			
Leu	Ser	Thr	Leu	Thr	Ile	Asp	Gly	Val	Thr	Arg	Ser	Asp	Gln	Gly	Leu
	290				295						300				
Tyr	Thr	Cys	Ala	Ala	Ser	Ser	Gly	Leu	Met	Thr	Lys	Lys	Asn	Ser	Thr
305					310					315				320	
Phe	Val	Arg	Val	His	Glu	Lys	Pro	Phe	Val	Ala	Phe	Gly	Ser	Gly	Met
			325						330					335	
Glu	Ser	Leu	Val	Glu	Ala	Thr	Val	Gly	Glu	Arg	Val	Arg	Ile	Pro	Ala
		340						345					350		
Lys	Tyr	Leu	Gly	Tyr	Pro	Pro	Pro	Glu	Ile	Lys	Trp	Tyr	Lys	Asn	Gly
	355						360					365			
Ile	Pro	Leu	Glu	Ser	Asn	His	Thr	Ile	Lys	Ala	Gly	His	Val	Leu	Thr
	370					375					380				
Ile	Met	Glu	Val	Ser	Glu	Arg	Asp	Thr	Gly	Asn	Tyr	Thr	Val	Ile	Leu
385					390					395				400	
Thr	Asn	Pro	Ile	Ser	Lys	Glu	Lys	Gln	Ser	His	Val	Val	Ser	Leu	Val
			405						410					415	
Val	Tyr	Val	Pro	Pro	Gln	Ile	Gly	Glu	Lys	Ser	Leu	Ile	Ser	Pro	Val
		420						425					430		
Asp	Ser	Tyr	Gln	Tyr	Gly	Thr	Thr	Gln	Thr	Leu	Thr	Cys	Thr	Val	Tyr
		435					440					445			
Ala	Ile	Pro	Pro	Pro	His	His	Ile	His	Trp	Tyr	Trp	Gln	Leu	Glu	Glu
	450					455					460				
Glu	Cys	Ala	Asn	Glu	Pro	Ser	Gln	Ala	Val	Ser	Val	Thr	Asn	Pro	Tyr
465					470					475				480	
Pro	Cys	Glu	Glu	Trp	Arg	Ser	Val	Glu	Asp	Phe	Gln	Gly	Gly	Asn	Lys
			485						490					495	
Ile	Glu	Val	Asn	Lys	Asn	Gln	Phe	Ala	Leu	Ile	Glu	Gly	Lys	Asn	Lys
		500						505					510		
Thr	Val	Ser	Thr	Leu	Val	Ile	Gln	Ala	Ala	Asn	Val	Ser	Ala	Leu	Tyr
	515						520					525			
Lys	Cys	Glu	Ala	Val	Asn	Lys	Val	Gly	Arg	Gly	Glu	Arg	Val	Ile	Ser
	530					535					540				
Phe	His	Val	Thr	Arg	Gly	Pro	Glu	Ile	Thr	Leu	Gln	Pro	Asp	Met	Gln
545					550					555				560	
Pro	Thr	Glu	Gln	Glu	Ser	Val	Ser	Leu	Trp	Cys	Thr	Ala	Asp	Arg	Ser
			565						570					575	
Thr	Phe	Glu	Asn	Leu	Thr	Trp	Tyr	Lys	Leu	Gly	Pro	Gln	Pro	Leu	Pro
			580					585					590		
Ile	His	Val	Gly	Glu	Leu	Pro	Thr	Pro	Val	Cys	Lys	Asn	Leu	Asp	Thr

				595				600					605			
Leu	Trp	Lys	Leu	Asn	Ala	Thr	Met	Phe	Ser	Asn	Ser	Thr	Asn	Asp	Ile	
	610						615					620				
Leu	Ile	Met	Glu	Leu	Lys	Asn	Ala	Ser	Leu	Gln	Asp	Gln	Gly	Asp	Tyr	
625					630					635					640	
Val	Cys	Leu	Ala	Gln	Asp	Arg	Lys	Thr	Lys	Lys	Arg	His	Cys	Val	Val	
				645					650					655		
Arg	Gln	Leu	Thr	Val	Leu	Glu	Arg	Val	Ala	Pro	Thr	Ile	Thr	Gly	Asn	
			660					665					670			
Leu	Glu	Asn	Gln	Thr	Thr	Ser	Ile	Gly	Glu	Ser	Ile	Glu	Val	Ser	Cys	
		675					680					685				
Thr	Ala	Ser	Gly	Asn	Pro	Pro	Pro	Gln	Ile	Met	Trp	Phe	Lys	Asp	Asn	
	690					695				700						
Glu	Thr	Leu	Val	Glu	Asp	Ser	Gly	Ile	Val	Leu	Lys	Asp	Gly	Asn	Arg	
705				710						715					720	
Asn	Leu	Thr	Ile	Arg	Arg	Val	Arg	Lys	Glu	Asp	Glu	Gly	Leu	Tyr	Thr	
				725					730					735		
Cys	Gln	Ala	Cys	Ser	Val	Leu	Gly	Cys	Ala	Lys	Val	Glu	Ala	Phe	Phe	
			740					745					750			
Ile	Ile	Glu	Gly	Ala	Gln	Glu	Lys	Thr	Asn	Leu	Glu	Ile	Ile	Ile	Leu	
		755					760					765				
Val	Gly	Thr	Ala	Val	Ile	Ala	Met	Phe	Phe	Trp	Leu	Leu	Leu	Val	Ile	
	770					775					780					
Ile	Leu	Arg	Thr	Val	Lys	Arg	Ala	Asn	Gly	Gly	Glu	Leu	Lys	Thr	Gly	
785					790					795					800	
Tyr	Leu	Ser	Ile	Val	Met	Asp	Pro	Asp	Glu	Leu	Pro	Leu	Asp	Glu	His	
				805					810					815		
Cys	Glu	Arg	Leu	Pro	Tyr	Asp	Ala	Ser	Lys	Trp	Glu	Phe	Pro	Arg	Asp	
			820					825					830			
Arg	Leu	Lys	Leu	Gly	Lys	Pro	Leu	Gly	Arg	Gly	Ala	Phe	Gly	Gln	Val	
			835				840					845				
Ile	Glu	Ala	Asp	Ala	Phe	Gly	Ile	Asp	Lys	Thr	Ala	Thr	Cys	Arg	Thr	
	850					855					860					
Val	Ala	Val	Lys	Met	Leu	Lys	Glu	Gly	Ala	Thr	His	Ser	Glu	His	Arg	
865					870					875					880	
Ala	Leu	Met	Ser	Glu	Leu	Lys	Ile	Leu	Ile	His	Ile	Gly	His	His	Leu	
				885					890					895		
Asn	Val	Val	Asn	Leu	Leu	Gly	Ala	Cys	Thr	Lys	Pro	Gly	Gly	Pro	Leu	
			900					905					910			
Met	Val	Ile	Val	Glu	Phe	Cys	Lys	Phe	Gly	Asn	Leu	Ser	Thr	Tyr	Leu	
		915					920					925				
Arg	Ser	Lys	Arg	Asn	Glu	Phe	Val	Pro	Tyr	Lys	Thr	Lys	Gly	Ala		

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      1045      1050      1055
Pro Asp Tyr Val Arg Lys Gly Asp Ala Arg Leu Pro Leu Lys Trp Met
      1060      1065      1070
Ala Pro Glu Thr Ile Phe Asp Arg Val Tyr Thr Ile Gln Ser Asp Val
      1075      1080      1085
Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Ser Leu Gly Ala Ser
      1090      1095      1100
Pro Tyr Pro Gly Val Lys Ile Asp Glu Glu Phe Cys Arg Arg Leu Lys
      1105      1110      1115      1120
Glu Gly Thr Arg Met Arg Ala Pro Asp Tyr Thr Thr Pro Glu Met Tyr
      1125      1130      1135
Gln Thr Met Leu Asp Cys Trp His Gly Glu Pro Ser Gln Arg Pro Thr
      1140      1145      1150
Phe Ser Glu Leu Val Glu His Leu Gly Asn Leu Leu Gln Ala Asn Ala
      1155      1160      1165
Gln Gln Asp Gly Lys Asp Tyr Ile Val Leu Pro Ile Ser Glu Thr Leu
      1170      1175      1180
Ser Met Glu Glu Asp Ser Gly Leu Ser Leu Pro Thr Ser Pro Val Ser
      1185      1190      1195      1200
Cys Met Glu Glu Glu Val Cys Asp Pro Lys Phe His Tyr Asp Asn
      1205      1210      1215
Thr Ala Gly Ile Ser Gln Tyr Leu Gln Asn Ser Lys Arg Lys Ser Arg
      1220      1225      1230
Pro Val Ser Val Lys Thr Phe Glu Asp Ile Pro Leu Glu Glu Pro Glu
      1235      1240      1245
Val Lys Val Ile Pro Asp Asp Asn Gln Thr Asp Ser Gly Met Val Leu
      1250      1255      1260
Ala Ser Glu Glu Leu Lys Thr Leu Glu Asp Arg Thr Lys Leu Ser Pro
      1265      1270      1275      1280
Ser Phe Gly Gly Met Val Pro Ser Lys Ser Arg Glu Ser Val Ala Ser
      1285      1290      1295
Glu Gly Ser Asn Gln Thr Ser Gly Tyr Gln Ser Gly Tyr His Ser Asp
      1300      1305      1310
Asp Thr Asp Thr Thr Val Tyr Ser Ser Glu Glu Ala Glu Leu Leu Lys
      1315      1320      1325
Leu Ile Glu Ile Gly Val Gln Thr Gly Ser Thr Ala Gln Ile Leu Gln
      1330      1335      1340
Pro Asp Ser Gly Thr Thr Leu Ser Ser Pro Pro Val
      1345      1350      1355

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<210> 284  
 <211> 1298  
 <212> PRT  
 <213> Homo sapiens

<300>  
 <308> GenBank No. NP002011  
 <309> 2004-12-18

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<400> 284
Met Gln Arg Gly Ala Ala Leu Cys Leu Arg Leu Trp Leu Cys Leu Gly
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Leu Leu Asp Gly Leu Val Ser Asp Tyr Ser Met Thr Pro Pro Thr Leu
      20           25           30
Asn Ile Thr Glu Glu Ser His Val Ile Asp Thr Gly Asp Ser Leu Ser

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		35					40					45						
Ile	Ser	Cys	Arg	Gly	Gln	His	Pro	Leu	Glu	Trp	Ala	Trp	Pro	Gly	Ala			
	50					55					60							
Gln	Glu	Ala	Pro	Ala	Thr	Gly	Asp	Lys	Asp	Ser	Glu	Asp	Thr	Gly	Val			
65					70					75					80			
Val	Arg	Asp	Cys	Glu	Gly	Thr	Asp	Ala	Arg	Pro	Tyr	Cys	Lys	Val	Leu			
			85						90					95				
Leu	Leu	His	Glu	Val	His	Ala	Asn	Asp	Thr	Gly	Ser	Tyr	Val	Cys	Tyr			
			100					105					110					
Tyr	Lys	Tyr	Ile	Lys	Ala	Arg	Ile	Glu	Gly	Thr	Thr	Ala	Ala	Ser	Ser			
		115					120					125						
Tyr	Val	Phe	Val	Arg	Asp	Phe	Glu	Gln	Pro	Phe	Ile	Asn	Lys	Pro	Asp			
		130				135					140							
Thr	Leu	Leu	Val	Asn	Arg	Lys	Asp	Ala	Met	Trp	Val	Pro	Cys	Leu	Val			
145					150					155					160			
Ser	Ile	Pro	Gly	Leu	Asn	Val	Thr	Leu	Arg	Ser	Gln	Ser	Ser	Val	Leu			
			165						170					175				
Trp	Pro	Asp	Gly	Gln	Glu	Val	Val	Trp	Asp	Asp	Arg	Arg	Gly	Met	Leu			
			180					185					190					
Val	Ser	Thr	Pro	Leu	Leu	His	Asp	Ala	Leu	Tyr	Leu	Gln	Cys	Glu	Thr			
		195					200					205						
Thr	Trp	Gly	Asp	Gln	Asp	Phe	Leu	Ser	Asn	Pro	Phe	Leu	Val	His	Ile			
		210				215						220						
Thr	Gly	Asn	Glu	Leu	Tyr	Asp	Ile	Gln	Leu	Leu	Pro	Arg	Lys	Ser	Leu			
225					230					235					240			
Glu	Leu	Leu	Val	Gly	Glu	Lys	Leu	Val	Leu	Asn	Cys	Thr	Val	Trp	Ala			
			245						250					255				
Glu	Phe	Asn	Ser	Gly	Val	Thr	Phe	Asp	Trp	Asp	Tyr	Pro	Gly	Lys	Gln			
			260					265					270					
Ala	Glu	Arg	Gly	Lys	Trp	Val	Pro	Glu	Arg	Arg	Ser	Gln	Gln	Thr	His			
		275					280					285						
Thr	Glu	Leu	Ser	Ser	Ile	Leu	Thr	Ile	His	Asn	Val	Ser	Gln	His	Asp			
		290				295					300							
Leu	Gly	Ser	Tyr	Val	Cys	Lys	Ala	Asn	Asn	Gly	Ile	Gln	Arg	Phe	Arg			
305					310					315					320			
Glu	Ser	Thr	Glu	Val	Ile	Val	His	Glu	Asn	Pro	Phe	Ile	Ser	Val	Glu			
			325						330					335				
Trp	Leu	Lys	Gly	Pro	Ile	Leu	Glu	Ala	Thr	Ala	Gly	Asp	Glu	Leu	Val			
			340					345					350					
Lys	Leu	Pro	Val	Lys	Leu	Ala	Ala	Tyr	Pro	Pro	Pro	Glu	Phe	Gln	Trp			
		355					360					365						
Tyr	Lys	Asp	Gly	Lys	Ala	Leu	Ser	Gly	Arg	His	Ser	Pro	His	Ala	Leu			
		370				375					380							
Val	Leu	Lys	Glu	Val	Thr	Glu	Ala	Ser	Thr	Gly	Thr	Tyr	Thr	Leu	Ala			
385					390					395								



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				485				490					495				
Ala	Val	Asn	Pro	Ile	Glu	Ser	Leu	Asp	Thr	Trp	Thr	Glu	Phe	Val	Glu		
			500					505					510				
Gly	Lys	Asn	Lys	Thr	Val	Ser	Lys	Leu	Val	Ile	Gln	Asn	Ala	Asn	Val		
		515					520					525					
Ser	Ala	Met	Tyr	Lys	Cys	Val	Val	Ser	Asn	Lys	Val	Gly	Gln	Asp	Glu		
		530				535					540						
Arg	Leu	Ile	Tyr	Phe	Tyr	Val	Thr	Thr	Ile	Pro	Asp	Gly	Phe	Thr	Ile		
545					550					555					560		
Glu	Ser	Lys	Pro	Ser	Glu	Glu	Leu	Leu	Glu	Gly	Gln	Pro	Val	Leu	Leu		
			565					570						575			
Ser	Cys	Gln	Ala	Asp	Ser	Tyr	Lys	Tyr	Glu	His	Leu	Arg	Trp	Tyr	Arg		
		580					585					590					
Leu	Asn	Leu	Ser	Thr	Leu	His	Asp	Ala	His	Gly	Asn	Pro	Leu	Leu	Leu		
		595				600					605						
Asp	Cys	Lys	Asn	Val	His	Leu	Phe	Ala	Thr	Pro	Leu	Ala	Ala	Ser	Leu		
	610				615						620						
Glu	Glu	Val	Ala	Pro	Gly	Ala	Arg	His	Ala	Thr	Leu	Ser	Leu	Ser	Ile		
625				630					635						640		
Pro	Arg	Val	Ala	Pro	Glu	His	Glu	Gly	His	Tyr	Val	Cys	Glu	Val	Gln		
			645					650						655			
Asp	Arg	Arg	Ser	His	Asp	Lys	His	Cys	His	Lys	Lys	Tyr	Leu	Ser	Val		
		660					665					670					
Gln	Ala	Leu	Glu	Ala	Pro	Arg	Leu	Thr	Gln	Asn	Leu	Thr	Asp	Leu	Leu		
	675					680					685						
Val	Asn	Val	Ser	Asp	Ser	Leu	Glu	Met	Gln	Cys	Leu	Val	Ala	Gly	Ala		
	690					695				700							
His	Ala	Pro	Ser	Ile	Val	Trp	Tyr	Lys	Asp	Glu	Arg	Leu	Leu	Glu	Glu		
705				710					715						720		
Lys	Ser	Gly	Val	Asp	Leu	Ala	Asp	Ser	Asn	Gln	Lys	Leu	Ser	Ile	Gln		
			725					730						735			
Arg	Val	Arg	Glu	Glu	Asp	Ala	Gly	Pro	Tyr	Leu	Cys	Ser	Val	Cys	Arg		
		740					745						750				
Pro	Lys	Gly	Cys	Val	Asn	Ser	Ser	Ala	Ser	Val	Ala	Val	Glu	Gly	Ser		
		755					760					765					
Glu	Asp	Lys	Gly	Ser	Met	Glu	Ile	Val	Ile	Leu	Val	Gly	Thr	Gly	Val		
	770					775				780							
Ile	Ala	Val	Phe	Phe	Trp	Val	Leu	Leu	Leu	Leu	Ile	Phe	Cys	Asn	Met		
785					790					795					800		
Arg	Arg	Pro	Ala	His	Ala	Asp	Ile	Lys	Thr	Gly	Tyr	Leu	Ser	Ile	Ile		
			805					810						815			
Met	Asp	Pro	Gly	Glu	Val	Pro	Leu	Glu	Glu	Gln	Cys	Glu	Tyr	Leu	Ser		
		820					825						830				
Tyr	Asp	Ala	Ser	Gln	Trp	Glu	Phe	Pro	Arg	Glu	Arg	Leu	His	Leu	Gly		
		835					840					845					
Arg	Val	Leu	Gly	Tyr	Gly	Ala	Phe	Gly	Lys	Val	Val	Glu	Ala	Ser	Ala		
	850					855				860							
Phe	Gly	Ile	His	Lys	Gly	Ser	Ser	Cys	Asp	Thr	Val	Ala	Val	Lys	Met		
865				870					875						880		
Leu	Lys	Glu	Gly	Ala	Thr	Ala	Ser	Glu	Gln	Arg	Ala	Leu	Met	Ser	Glu		
			885					890						895			
Leu	Lys	Ile	Leu	Ile	His	Ile	Gly	Asn	His	Leu	Asn	Val	Val	Asn	Leu		
		900					905						910				
Leu	Gly	Ala	Cys	Thr	Lys	Pro	Gln	Gly	Pro	Leu	Met	Val	Ile	Val	Glu		
		915					920					925					
Phe	Cys	Lys	Tyr	Gly	Asn	Leu	Ser	Asn	Phe	Leu	Arg	Ala	Lys	Arg	Asp		

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930	935	940
Ala Phe Ser Pro Cys	Ala Glu Lys Ser Pro Glu Gln Arg Gly Arg Phe	
945	950	955
Arg Ala Met Val Glu Leu Ala Arg Leu Asp Arg Arg Arg Pro Gly Ser		
965	970	975
Ser Asp Arg Val Leu Phe Ala Arg Phe Ser Lys Thr Glu Gly Gly Ala		
980	985	990
Arg Arg Ala Ser Pro Asp Gln Glu Ala Glu Asp Leu Trp Leu Ser Pro		
995	1000	1005
Leu Thr Met Glu Asp Leu Val Cys Tyr Ser Phe Gln Val Ala Arg Gly		
1010	1015	1020
Met Glu Phe Leu Ala Ser Arg Lys Cys Ile His Arg Asp Leu Ala Ala		
1025	1030	1035
Arg Asn Ile Leu Leu Ser Glu Ser Asp Val Val Lys Ile Cys Asp Phe		
1045	1050	1055
Gly Leu Ala Arg Asp Ile Tyr Lys Asp Pro Asp Tyr Val Arg Lys Gly		
1060	1065	1070
Ser Ala Arg Leu Pro Leu Lys Trp Met Ala Pro Glu Ser Ile Phe Asp		
1075	1080	1085
Lys Val Tyr Thr Thr Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu		
1090	1095	1100
Trp Glu Ile Phe Ser Leu Gly Ala Ser Pro Tyr Pro Gly Val Gln Ile		
1105	1110	1115
Asn Glu Glu Phe Cys Gln Arg Val Arg Asp Gly Thr Arg Met Arg Ala		
1125	1130	1135
Pro Glu Leu Ala Thr Pro Ala Ile Arg His Ile Met Leu Asn Cys Trp		
1140	1145	1150
Ser Gly Asp Pro Lys Ala Arg Pro Ala Phe Ser Asp Leu Val Glu Ile		
1155	1160	1165
Leu Gly Asp Leu Leu Gln Gly Arg Gly Leu Gln Glu Glu Glu Val		
1170	1175	1180
Cys Met Ala Pro Arg Ser Ser Gln Ser Ser Glu Glu Gly Ser Phe Ser		
1185	1190	1195
Gln Val Ser Thr Met Ala Leu His Ile Ala Gln Ala Asp Ala Glu Asp		
1205	1210	1215
Ser Pro Pro Ser Leu Gln Arg His Ser Leu Ala Ala Arg Tyr Tyr Asn		
1220	1225	1230
Trp Val Ser Phe Pro Gly Cys Leu Ala Arg Gly Ala Glu Thr Arg Gly		
1235	1240	1245
Ser Ser Arg Met Lys Thr Phe Glu Glu Phe Pro Met Thr Pro Thr Thr		
1250	1255	1260
Tyr Lys Gly Ser Val Asp Asn Gln Thr Asp Ser Gly Met Val Leu Ala		
1265	1270	1275
Ser Glu Glu Phe Glu Gln Ile Glu Ser Arg His Arg Gln Glu Ser Gly		
1285	1290	1295
Phe Arg		

<210> 285  
 <211> 972  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT

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&lt;222&gt; 279

&lt;223&gt; Xaa = V or M

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 362

&lt;223&gt; Xaa = H or R

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 969

&lt;223&gt; Xaa = Y or C

&lt;400&gt; 285

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Gly Gln Gly Ile Pro Val Ile Glu Pro Ser Val Pro Glu Leu Val Val
 20      25      30
Lys Pro Gly Ala Thr Val Thr Leu Arg Cys Val Gly Asn Gly Ser Val
 35      40      45
Glu Trp Asp Gly Pro Pro Ser Pro His Trp Thr Leu Tyr Ser Asp Gly
 50      55      60
Ser Ser Ser Ile Leu Ser Thr Asn Asn Ala Thr Phe Gln Asn Thr Gly
 65      70      75      80
Thr Tyr Arg Cys Thr Glu Pro Gly Asp Pro Leu Gly Gly Ser Ala Ala
 85      90      95
Ile His Leu Tyr Val Lys Asp Pro Ala Arg Pro Trp Asn Val Leu Ala
 100     105     110
Gln Glu Val Val Phe Glu Asp Gln Asp Ala Leu Leu Pro Cys Leu
 115     120     125
Leu Thr Asp Pro Val Leu Glu Ala Gly Val Ser Leu Val Arg Val Arg
 130     135     140
Gly Arg Pro Leu Met Arg His Thr Asn Tyr Ser Phe Ser Pro Trp His
 145     150     155     160
Gly Phe Thr Ile His Arg Ala Lys Phe Ile Gln Ser Gln Asp Tyr Gln
 165     170     175
Cys Ser Ala Leu Met Gly Gly Arg Lys Val Met Ser Ile Ser Ile Arg
 180     185     190
Leu Lys Val Gln Lys Val Ile Pro Gly Pro Pro Ala Leu Thr Leu Val
 195     200     205
Pro Ala Glu Leu Val Arg Ile Arg Gly Glu Ala Ala Gln Ile Val Cys
 210     215     220
Ser Ala Ser Ser Val Asp Val Asn Phe Asp Val Phe Leu Gln His Asn
 225     230     235     240
Asn Thr Lys Leu Ala Ile Pro Gln Gln Ser Asp Phe His Asn Asn Arg
 245     250     255
Tyr Gln Lys Val Leu Thr Leu Asn Leu Asp Gln Val Asp Phe Gln His
 260     265     270
Ala Gly Asn Tyr Ser Cys Xaa Ala Ser Asn Val Gln Gly Lys His Ser
 275     280     285
Thr Ser Met Phe Phe Arg Val Glu Ser Ala Tyr Leu Asn Leu Ser
 290     295     300
Ser Glu Gln Asn Leu Ile Gln Glu Val Thr Val Gly Glu Gly Leu Asn
 305     310     315     320
Leu Lys Val Met Val Glu Ala Tyr Pro Gly Leu Gln Gly Phe Asn Trp
 325     330     335

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Thr Tyr Leu Gly Pro Phe Ser Asp His Gln Pro Glu Pro Lys Leu Ala  
 340 345 350  
 Asn Ala Thr Thr Lys Asp Thr Tyr Arg Xaa Thr Phe Thr Leu Ser Leu  
 355 360 365  
 Pro Arg Leu Lys Pro Ser Glu Ala Gly Arg Tyr Ser Phe Leu Ala Arg  
 370 375 380  
 Asn Pro Gly Gly Trp Arg Ala Leu Thr Phe Glu Leu Thr Leu Arg Tyr  
 385 390 395 400  
 Pro Pro Glu Val Ser Val Ile Trp Thr Phe Ile Asn Gly Ser Gly Thr  
 405 410 415  
 Leu Leu Cys Ala Ala Ser Gly Tyr Pro Gln Pro Asn Val Thr Trp Leu  
 420 425 430  
 Gln Cys Ser Gly His Thr Asp Arg Cys Asp Glu Ala Gln Val Leu Gln  
 435 440 445  
 Val Trp Asp Asp Pro Tyr Pro Glu Val Leu Ser Gln Glu Pro Phe His  
 450 455 460  
 Lys Val Thr Val Gln Ser Leu Leu Thr Val Glu Thr Leu Glu His Asn  
 465 470 475 480  
 Gln Thr Tyr Glu Cys Arg Ala His Asn Ser Val Gly Ser Gly Ser Trp  
 485 490 495  
 Ala Phe Ile Pro Ile Ser Ala Gly Ala His Thr His Pro Pro Asp Glu  
 500 505 510  
 Phe Leu Phe Thr Pro Val Val Val Ala Cys Met Ser Ile Met Ala Leu  
 515 520 525  
 Leu Leu Leu Leu Leu Leu Leu Tyr Lys Tyr Lys Gln Lys Pro  
 530 535 540  
 Lys Tyr Gln Val Arg Trp Lys Ile Ile Glu Ser Tyr Glu Gly Asn Ser  
 545 550 555 560  
 Tyr Thr Phe Ile Asp Pro Thr Gln Leu Pro Tyr Asn Glu Lys Trp Glu  
 565 570 575  
 Phe Pro Arg Asn Asn Leu Gln Phe Gly Lys Thr Leu Gly Ala Gly Ala  
 580 585 590  
 Phe Gly Lys Val Val Glu Ala Thr Ala Phe Gly Leu Gly Lys Glu Asp  
 595 600 605  
 Ala Val Leu Lys Val Ala Val Lys Met Leu Lys Ser Thr Ala His Ala  
 610 615 620  
 Asp Glu Lys Glu Ala Leu Met Ser Glu Leu Lys Ile Met Ser His Leu  
 625 630 635 640  
 Gly Gln His Glu Asn Ile Val Asn Leu Leu Gly Ala Cys Thr His Gly  
 645 650 655  
 Gly Pro Val Leu Val Ile Thr Glu Tyr Cys Cys Tyr Gly Asp Leu Leu  
 660 665 670  
 Asn Phe Leu Arg Arg Lys Ala Glu Ala Met Leu Gly Pro Ser Leu Ser  
 675 680 685  
 Pro Gly Gln Asp Pro Glu Gly Gly Val Asp Tyr Lys Asn Ile His Leu  
 690 695 700  
 Glu Lys Lys Tyr Val Arg Arg Asp Ser Gly Phe Ser Ser Gln Gly Val  
 705 710 715 720  
 Asp Thr Tyr Val Glu Met Arg Pro Val Ser Thr Ser Ser Asn Asp Ser  
 725 730 735  
 Phe Ser Glu Gln Asp Leu Asp Lys Glu Asp Gly Arg Pro Leu Glu Leu  
 740 745 750  
 Arg Asp Leu Leu His Phe Ser Ser Gln Val Ala Gln Gly Met Ala Phe  
 755 760 765  
 Leu Ala Ser Lys Asn Cys Ile His Arg Asp Val Ala Ala Arg Asn Val  
 770 775 780

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Leu Leu Thr Asn Gly His Val Ala Lys Ile Gly Asp Phe Gly Leu Ala
785              790              795              800
Arg Asp Ile Met Asn Asp Ser Asn Tyr Ile Val Lys Gly Asn Ala Arg
              805              810              815
Leu Pro Val Lys Trp Met Ala Pro Glu Ser Ile Phe Asp Cys Val Tyr
              820              825              830
Thr Val Gln Ser Asp Val Trp Ser Tyr Gly Ile Leu Leu Trp Glu Ile
              835              840              845
Phe Ser Leu Gly Leu Asn Pro Tyr Pro Gly Ile Leu Val Asn Ser Lys
              850              855              860
Phe Tyr Lys Leu Val Lys Asp Gly Tyr Gln Met Ala Gln Pro Ala Phe
865              870              875              880
Ala Pro Lys Asn Ile Tyr Ser Ile Met Gln Ala Cys Trp Ala Leu Glu
              885              890              895
Pro Thr His Arg Pro Thr Phe Gln Gln Ile Cys Ser Phe Leu Gln Glu
              900              905              910
Gln Ala Gln Glu Asp Arg Arg Glu Arg Asp Tyr Thr Asn Leu Pro Ser
              915              920              925
Ser Ser Arg Ser Gly Gly Ser Gly Ser Ser Ser Ser Glu Leu Glu Glu
              930              935              940
Glu Ser Ser Ser Glu His Leu Thr Cys Cys Glu Gln Gly Asp Ile Ala
945              950              955              960
Gln Pro Leu Leu Gln Pro Asn Asn Xaa Gln Phe Cys
              965              970

```

<210> 286  
 <211> 913  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 53  
 <223> Xaa = W or A

<220>  
 <221> VARIANT  
 <222> 55, 68  
 <223> Xaa = D or A

<220>  
 <221> VARIANT  
 <222> 66, 175  
 <223> Xaa = S or A

<220>  
 <221> VARIANT  
 <222> 105  
 <223> Xaa = R or A

<220>  
 <221> VARIANT  
 <222> 106  
 <223> Xaa = H or A

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<220>  
 <221> VARIANT  
 <222> 110  
 <223> Xaa = L or A

<220>  
 <221> VARIANT  
 <222> 112  
 <223> Xaa = K or A

<220>  
 <221> VARIANT  
 <222> 173  
 <223> Xaa = V or A

<220>  
 <221> VARIANT  
 <222> 174  
 <223> Xaa = M or A

<400> 286  
 Met Gly Pro Glu Ala Leu Ser Ser Leu Leu Leu Leu Leu Val Ala  
 1 5 10 15  
 Ser Gly Asp Ala Asp Met Lys Gly His Phe Asp Pro Ala Lys Cys Arg  
 20 25 30  
 Tyr Ala Leu Gly Met Gln Asp Arg Thr Ile Pro Asp Ser Asp Ile Ser  
 35 40 45  
 Ala Ser Ser Ser Xaa Ser Xaa Ser Thr Ala Ala Arg His Ser Arg Leu  
 50 55 60  
 Glu Xaa Ser Xaa Gly Asp Gly Ala Trp Cys Pro Ala Gly Ser Val Phe  
 65 70 75 80  
 Pro Lys Glu Glu Glu Tyr Leu Gln Val Asp Leu Gln Arg Leu His Leu  
 85 90 95  
 Val Ala Leu Val Gly Thr Gln Gly Xaa Xaa Ala Gly Gly Xaa Gly Xaa  
 100 105 110  
 Glu Phe Ser Arg Ser Tyr Arg Leu Arg Tyr Ser Arg Asp Gly Arg Arg  
 115 120 125  
 Trp Met Gly Trp Lys Asp Arg Trp Gly Gln Glu Val Ile Ser Gly Asn  
 130 135 140  
 Glu Asp Pro Glu Gly Val Val Leu Lys Asp Leu Gly Pro Pro Met Val  
 145 150 155 160  
 Ala Arg Leu Val Arg Phe Tyr Pro Arg Ala Asp Arg Xaa Xaa Xaa Val  
 165 170 175  
 Cys Leu Arg Val Glu Leu Tyr Gly Cys Leu Trp Arg Asp Gly Leu Leu  
 180 185 190  
 Ser Tyr Thr Ala Pro Val Gly Gln Thr Met Tyr Leu Ser Glu Ala Val  
 195 200 205  
 Tyr Leu Asn Asp Ser Thr Tyr Asp Gly His Thr Val Gly Gly Leu Gln  
 210 215 220  
 Tyr Gly Gly Leu Gly Gln Leu Ala Asp Gly Val Val Gly Leu Asp Asp  
 225 230 235 240  
 Phe Arg Lys Ser Gln Glu Leu Arg Val Trp Pro Gly Tyr Asp Tyr Val  
 245 250 255  
 Gly Trp Ser Asn His Ser Phe Ser Ser Gly Tyr Val Glu Met Glu Phe  
 260 265 270  
 Glu Phe Asp Arg Leu Arg Ala Phe Gln Ala Met Gln Val His Cys Asn

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275	280	285
Asn Met His Thr Leu Gly	Ala Arg Leu Pro Gly Gly	Val Glu Cys Arg
290	295	300
Phe Arg Arg Gly Pro	Ala Met Ala Trp Glu Gly	Glu Pro Met Arg His
305	310	315
Asn Leu Gly Gly Asn Leu Gly	Asp Pro Arg Ala Arg	Ala Val Ser Val
325	330	335
Pro Leu Gly Gly Arg Val	Ala Arg Phe Leu Gln Cys	Arg Phe Leu Phe
340	345	350
Ala Gly Pro Trp Leu Leu Phe	Ser Glu Ile Ser Phe	Ile Ser Asp Val
355	360	365
Val Asn Asn Ser Ser Pro	Ala Leu Gly Gly Thr	Phe Pro Pro Ala Pro
370	375	380
Trp Trp Pro Pro Gly	Pro Pro Pro Thr Asn	Phe Ser Ser Leu Glu Leu
385	390	395
Glu Pro Arg Gly Gln	Gln Pro Val Ala Lys	Ala Glu Gly Ser Pro Thr
405	410	415
Ala Ile Leu Ile Gly	Cys Leu Val Ala Ile	Ile Leu Leu Leu Leu
420	425	430
Ile Ile Ala Leu Met	Leu Trp Arg Leu His	Trp Arg Arg Leu Leu Ser
435	440	445
Lys Ala Glu Arg Arg	Val Leu Glu Glu Leu	Thr Val His Leu Ser
450	455	460
Val Pro Gly Asp Thr	Ile Leu Ile Asn Asn	Arg Pro Gly Pro Arg Glu
465	470	475
Pro Pro Pro Tyr Gln	Glu Pro Arg Pro Arg	Gly Asn Pro Pro His Ser
485	490	495
Ala Pro Cys Val Pro	Asn Gly Ser Ala Leu	Leu Leu Ser Asn Pro Ala
500	505	510
Tyr Arg Leu Leu Ala	Thr Tyr Ala Arg Pro	Pro Arg Gly Pro Gly
515	520	525
Pro Pro Thr Pro Ala	Trp Ala Lys Pro Thr	Asn Thr Gln Ala Tyr Ser
530	535	540
Gly Asp Tyr Met Glu	Pro Glu Lys Pro Gly	Ala Pro Leu Leu Pro Pro
545	550	555
Pro Pro Gln Asn Ser	Val Pro His Tyr Ala	Glu Ala Asp Ile Val Thr
565	570	575
Leu Gln Gly Val Thr	Gly Gly Asn Thr Tyr	Ala Val Pro Ala Leu Pro
580	585	590
Pro Gly Ala Val Gly	Asp Gly Pro Pro Arg	Val Asp Phe Pro Arg Ser
595	600	605
Arg Leu Arg Phe Lys	Glu Lys Leu Gly Glu	Gly Gln Phe Gly Glu Val
610	615	620
His Leu Cys Glu Val	Asp Ser Pro Gln Asp	Leu Val Ser Leu Asp Phe
625	630	635
Pro Leu Asn Val Arg	Lys Gly His Pro Leu	Leu Val Ala Val Lys Ile
645	650	655
Leu Arg Pro Asp Ala	Thr Lys Asn Ala Arg	Asn Asp Phe Leu Lys Glu
660	665	670
Val Lys Ile Met Ser	Arg Leu Lys Asp Pro	Asn Ile Ile Arg Leu Leu
675	680	685
Gly Val Cys Val Gln	Asp Asp Pro Leu Cys	Met Ile Thr Asp Tyr Met
690	695	700
Glu Asn Gly Asp Leu	Asn Gln Phe Leu Ser	Ala His Gln Leu Glu Asp
705	710	715
Lys Ala Ala Glu Gly	Ala Pro Gly Asp Gly	Gln Ala Ala Gln Gly Pro

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[illegible]

```
<210> 287
<211> 855
<212> PRT
<213> Homo sapiens
```

```
<220>  
<221> VARIANT  
<222> 550  
<223> Xaa = G or R
```

<400> 287															
Met	Ile	Leu	Ile	Pro	Arg	Met	Leu	Leu	Val	Leu	Phe	Leu	Leu	Leu	Pro
1				5					10					15	
Ile	Leu	Ser	Ser	Ala	Lys	Ala	Gln	Val	Asn	Pro	Ala	Ile	Cys	Arg	Tyr
			20					25					30		
Pro	Leu	Gly	Met	Ser	Gly	Gly	Gln	Ile	Pro	Asp	Glu	Asp	Ile	Thr	Ala
		35					40					45			
Ser	Ser	Gln	Trp	Ser	Glu	Ser	Thr	Ala	Ala	Lys	Tyr	Gly	Arg	Leu	Asp
	50					55					60				
Ser	Glu	Glu	Gly	Asp	Gly	Ala	Trp	Cys	Pro	Glu	Ile	Pro	Val	Glu	Pro
65				70						75				80	
Asp	Asp	Leu	Lys	Glu	Phe	Leu	Gln	Ile	Asp	Leu	His	Thr	Leu	His	Phe
			85						90					95	
Ile	Thr	Leu	Val	Gly	Thr	Gln	Gly	Arg	His	Ala	Gly	Gly	His	Gly	Ile
			100					105					110		
Glu	Phe	Ala	Pro	Met	Tyr	Lys	Ile	Asn	Tyr	Ser	Arg	Asp	Gly	Thr	Arg
		115					120					125			
Trp	Ile	Ser	Trp	Arg	Asn	Arg	His	Gly	Lys	Gln	Val	Leu	Asp	Gly	Asn
	130					135					140				



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Ser Asn Pro Tyr Asp Ile Phe Leu Lys Asp Leu Glu Pro Pro Ile Val  
 145 150 155 160  
 Ala Arg Phe Val Arg Phe Ile Pro Val Thr Asp His Ser Met Asn Val  
 165 170 175  
 Cys Met Arg Val Glu Leu Tyr Gly Cys Val Trp Leu Asp Gly Leu Val  
 180 185 190  
 Ser Tyr Asn Ala Pro Ala Gly Gln Phe Val Leu Pro Gly Gly Ser  
 195 200 205  
 Ile Ile Tyr Leu Asn Asp Ser Val Tyr Asp Gly Ala Val Gly Tyr Ser  
 210 215 220  
 Met Thr Glu Gly Leu Gly Gln Leu Thr Asp Gly Val Ser Gly Leu Asp  
 225 230 235 240  
 Asp Phe Thr Gln Thr His Glu Tyr His Val Trp Pro Gly Tyr Asp Tyr  
 245 250 255  
 Val Gly Trp Arg Asn Glu Ser Ala Thr Asn Gly Tyr Ile Glu Ile Met  
 260 265 270  
 Phe Glu Phe Asp Arg Ile Arg Asn Phe Thr Thr Met Lys Val His Cys  
 275 280 285  
 Asn Asn Met Phe Ala Lys Gly Val Lys Ile Phe Lys Glu Val Gln Cys  
 290 295 300  
 Tyr Phe Arg Ser Glu Ala Ser Glu Trp Glu Pro Asn Ala Ile Ser Phe  
 305 310 315 320  
 Pro Leu Val Leu Asp Asp Val Asn Pro Ser Ala Arg Phe Val Thr Val  
 325 330 335  
 Pro Leu His His Arg Met Ala Ser Ala Ile Lys Cys Gln Tyr His Phe  
 340 345 350  
 Ala Asp Thr Trp Met Met Phe Ser Glu Ile Thr Phe Gln Ser Asp Ala  
 355 360 365  
 Ala Met Tyr Asn Asn Ser Glu Ala Leu Pro Thr Ser Pro Met Ala Pro  
 370 375 380  
 Thr Thr Tyr Asp Pro Met Leu Lys Val Asp Asp Ser Asn Thr Arg Ile  
 385 390 395 400  
 Leu Ile Gly Cys Leu Val Ala Ile Ile Phe Ile Leu Leu Ala Ile Ile  
 405 410 415  
 Val Ile Ile Leu Trp Arg Gln Phe Trp Gln Lys Met Leu Glu Lys Ala  
 420 425 430  
 Ser Arg Arg Met Leu Asp Asp Glu Met Thr Val Ser Leu Ser Leu Pro  
 435 440 445  
 Ser Asp Ser Ser Met Phe Asn Asn Asn Arg Ser Ser Pro Ser Glu  
 450 455 460  
 Gln Gly Ser Asn Ser Thr Tyr Asp Arg Ile Phe Pro Leu Arg Pro Asp  
 465 470 475 480  
 Tyr Gln Glu Pro Ser Arg Leu Ile Arg Lys Leu Pro Glu Phe Ala Pro  
 485 490 495  
 Gly Glu Glu Glu Ser Gly Cys Ser Gly Val Val Lys Pro Val Gln Pro  
 500 505 510  
 Ser Gly Pro Glu Gly Val Pro His Tyr Ala Glu Ala Asp Ile Val Asn  
 515 520 525  
 Leu Gln Gly Val Thr Gly Gly Asn Thr Tyr Ser Val Pro Ala Val Thr  
 530 535 540  
 Met Asp Leu Leu Ser Xaa Lys Asp Val Ala Val Glu Glu Phe Pro Arg  
 545 550 555 560  
 Lys Leu Leu Thr Phe Lys Glu Lys Leu Gly Glu Gly Gln Phe Gly Glu  
 565 570 575  
 Val His Leu Cys Glu Val Glu Gly Met Glu Lys Phe Lys Asp Lys Asp  
 580 585 590

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Phe Ala Leu Asp Val Ser Ala Asn Gln Pro Val Leu Val Ala Val Lys
    595                      600                      605
Met Leu Arg Ala Asp Ala Asn Lys Asn Ala Arg Asn Asp Phe Leu Lys
    610                      615                      620
Glu Ile Lys Ile Met Ser Arg Leu Lys Asp Pro Asn Ile Ile His Leu
    625                      630                      635                      640
Leu Ser Val Cys Ile Thr Asp Asp Pro Leu Cys Met Ile Thr Glu Tyr
    645                      650                      655
Met Glu Asn Gly Asp Leu Asn Gln Phe Leu Ser Arg His Glu Pro Pro
    660                      665                      670
Asn Ser Ser Ser Ser Asp Val Arg Thr Val Ser Tyr Thr Asn Leu Lys
    675                      680                      685
Phe Met Ala Thr Gln Ile Ala Ser Gly Met Lys Tyr Leu Ser Ser Leu
    690                      695                      700
Asn Phe Val His Arg Asp Leu Ala Thr Arg Asn Cys Leu Val Gly Lys
    705                      710                      715                      720
Asn Tyr Thr Ile Lys Ile Ala Asp Phe Gly Met Ser Arg Asn Leu Tyr
    725                      730                      735
Ser Gly Asp Tyr Tyr Arg Ile Gln Gly Arg Ala Val Leu Pro Ile Arg
    740                      745                      750
Trp Met Ser Trp Glu Ser Ile Leu Leu Gly Lys Phe Thr Thr Ala Ser
    755                      760                      765
Asp Val Trp Ala Phe Gly Val Thr Leu Trp Glu Thr Phe Thr Phe Cys
    770                      775                      780
Gln Glu Gln Pro Tyr Ser Gln Leu Ser Asp Glu Gln Val Ile Glu Asn
    785                      790                      795                      800
Thr Gly Glu Phe Phe Arg Asp Gln Gly Arg Gln Thr Tyr Leu Pro Gln
    805                      810                      815
Pro Ala Ile Cys Pro Asp Ser Val Tyr Lys Leu Met Leu Ser Cys Trp
    820                      825                      830
Arg Arg Asp Thr Lys Asn Arg Pro Ser Phe Gln Glu Ile His Leu Leu
    835                      840                      845
Leu Leu Gln Gln Gly Asp Glu
    850                      855

```

<210> 288  
 <211> 1210  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 521  
 <223> Xaa = R or K

```

<400> 288
Met Arg Pro Ser Gly Thr Ala Gly Ala Ala Leu Leu Ala Leu Leu Ala
  1          5          10          15
Ala Leu Cys Pro Ala Ser Arg Ala Leu Glu Glu Lys Lys Val Cys Gln
    20          25          30
Gly Thr Ser Asn Lys Leu Thr Gln Leu Gly Thr Phe Glu Asp His Phe
    35          40          45
Leu Ser Leu Gln Arg Met Phe Asn Asn Cys Glu Val Val Leu Gly Asn
    50          55          60
Leu Glu Ile Thr Tyr Val Gln Arg Asn Tyr Asp Leu Ser Phe Leu Lys

```

65					70					75					80		
Thr	Ile	Gln	Glu	Val	Ala	Gly	Tyr	Val	Leu	Ile	Ala	Leu	Asn	Thr	Val		
				85					90					95			
Glu	Arg	Ile	Pro	Leu	Glu	Asn	Leu	Gln	Ile	Ile	Arg	Gly	Asn	Met	Tyr		
				100					105					110			
Tyr	Glu	Asn	Ser	Tyr	Ala	Leu	Ala	Val	Leu	Ser	Asn	Tyr	Asp	Ala	Asn		
				115					120					125			
Lys	Thr	Gly	Leu	Lys	Glu	Leu	Pro	Met	Arg	Asn	Leu	Gln	Glu	Ile	Leu		
				130					135					140			
His	Gly	Ala	Val	Arg	Phe	Ser	Asn	Asn	Pro	Ala	Leu	Cys	Asn	Val	Glu		
145					150					155					160		
Ser	Ile	Gln	Trp	Arg	Asp	Ile	Val	Ser	Ser	Asp	Phe	Leu	Ser	Asn	Met		
				165					170					175			
Ser	Met	Asp	Phe	Gln	Asn	His	Leu	Gly	Ser	Cys	Gln	Lys	Cys	Asp	Pro		
				180					185					190			
Ser	Cys	Pro	Asn	Gly	Ser	Cys	Trp	Gly	Ala	Gly	Glu	Glu	Asn	Cys	Gln		
				195					200					205			
Lys	Leu	Thr	Lys	Ile	Ile	Cys	Ala	Gln	Gln	Cys	Ser	Gly	Arg	Cys	Arg		
				210					215					220			
Gly	Lys	Ser	Pro	Ser	Asp	Cys	Cys	His	Asn	Gln	Cys	Ala	Ala	Gly	Cys		
225					230					235					240		
Thr	Gly	Pro	Arg	Glu	Ser	Asp	Cys	Leu	Val	Cys	Arg	Lys	Phe	Arg	Asp		
				245					250					255			
Glu	Ala	Thr	Cys	Lys	Asp	Thr	Cys	Pro	Pro	Leu	Met	Leu	Tyr	Asn	Pro		
				260					265					270			
Thr	Thr	Tyr	Gln	Met	Asp	Val	Asn	Pro	Glu	Gly	Lys	Tyr	Ser	Phe	Gly		
				275					280					285			
Ala	Thr	Cys	Val	Lys	Lys	Cys	Pro	Arg	Asn	Tyr	Val	Val	Thr	Asp	His		
				290					295					300			
Gly	Ser	Cys	Val	Arg	Ala	Cys	Gly	Ala	Asp	Ser	Tyr	Glu	Met	Glu	Glu		
305					310					315					320		
Asp	Gly	Val	Arg	Lys	Cys	Lys	Lys	Cys	Glu	Gly	Pro	Cys	Arg	Lys	Val		
				325					330					335			
Cys	Asn	Gly	Ile	Gly	Ile	Gly	Glu	Phe	Lys	Asp	Ser	Leu	Ser	Ile	Asn		
				340					345					350			
Ala	Thr	Asn	Ile	Lys	His	Phe	Lys	Asn	Cys	Thr	Ser	Ile	Ser	Gly	Asp		
				355					360					365			
Leu	His	Ile	Leu	Pro	Val	Ala	Phe	Arg	Gly	Asp	Ser	Phe	Thr	His	Thr		
				370					375					380			
Pro	Pro	Leu	Asp	Pro	Gln	Glu	Leu	Asp	Ile	Leu	Lys	Thr	Val	Lys	Glu		
385					390					395					400		
Ile	Thr	Gly	Phe	Leu	Leu	Ile	Gln	Ala	Trp	Pro	Glu	Asn	Arg	Thr	Asp		
				405					410					415			
Leu	His	Ala	Phe	Glu	Asn	Leu	Glu	Ile	Ile	Arg	Gly	Arg	Thr	Lys	Gln		
				420					425					430			
His	Gly	Gln	Phe	Ser	Leu	Ala	Val	Val	Ser	Leu	Asn	Ile	Thr	Ser	Leu		
				435					440					445			
Gly	Leu	Arg	Ser	Leu	Lys	Glu	Ile	Ser	Asp	Gly	Asp	Val	Ile	Ile	Ser		
				450					455					460			
Gly	Asn	Lys	Asn	Leu	Cys	Tyr	Ala	Asn	Thr	Ile	Asn	Trp	Lys	Lys	Leu		
465					470					475					480		

	515						520						525					
Val	Ser	Arg	Gly	Arg	Glu	Cys	Val	Asp	Lys	Cys	Asn	Leu	Leu	Glu	Gly			
	530					535					540							
Glu	Pro	Arg	Glu	Phe	Val	Glu	Asn	Ser	Glu	Cys	Ile	Gln	Cys	His	Pro			
545					550					555					560			
Glu	Cys	Leu	Pro	Gln	Ala	Met	Asn	Ile	Thr	Cys	Thr	Gly	Arg	Gly	Pro			
				565					570					575				
Asp	Asn	Cys	Ile	Gln	Cys	Ala	His	Tyr	Ile	Asp	Gly	Pro	His	Cys	Val			
			580					585					590					
Lys	Thr	Cys	Pro	Ala	Gly	Val	Met	Gly	Glu	Asn	Asn	Thr	Leu	Val	Trp			
		595					600					605						
Lys	Tyr	Ala	Asp	Ala	Gly	His	Val	Cys	His	Leu	Cys	His	Pro	Asn	Cys			
	610					615					620							
Thr	Tyr	Gly	Cys	Thr	Gly	Pro	Gly	Leu	Glu	Gly	Cys	Pro	Thr	Asn	Gly			
625					630					635					640			
Pro	Lys	Ile	Pro	Ser	Ile	Ala	Thr	Gly	Met	Val	Gly	Ala	Leu	Leu	Leu			
				645					650					655				
Leu	Leu	Val	Val	Ala	Leu	Gly	Ile	Gly	Leu	Phe	Met	Arg	Arg	Arg	His			
			660					665					670					
Ile	Val	Arg	Lys	Arg	Thr	Leu	Arg	Arg	Leu	Leu	Gln	Glu	Arg	Glu	Leu			
			675				680					685						
Val	Glu	Pro	Leu	Thr	Pro	Ser	Gly	Glu	Ala	Pro	Asn	Gln	Ala	Leu	Leu			
	690					695					700							
Arg	Ile	Leu	Lys	Glu	Thr	Glu	Phe	Lys	Lys	Ile	Lys	Val	Leu	Gly	Ser			
705					710					715					720			
Gly	Ala	Phe	Gly	Thr	Val	Tyr	Lys	Gly	Leu	Trp	Ile	Pro	Glu	Gly	Glu			
				725					730					735				
Lys	Val	Lys	Ile	Pro	Val	Ala	Ile	Lys	Glu	Leu	Arg	Glu	Ala	Thr	Ser			
			740					745					750					
Pro	Lys	Ala	Asn	Lys	Glu	Ile	Leu	Asp	Glu	Ala	Tyr	Val	Met	Ala	Ser			
		755					760					765						
Val	Asp	Asn	Pro	His	Val	Cys	Arg	Leu	Leu	Gly	Ile	Cys	Leu	Thr	Ser			
	770					775					780							
Thr	Val	Gln	Leu	Ile	Thr	Gln	Leu	Met	Pro	Phe	Gly	Cys	Leu	Leu	Asp			
785					790					795					800			
Tyr	Val	Arg	Glu	His	Lys	Asp	Asn	Ile	Gly	Ser	Gln	Tyr	Leu	Leu	Asn			
				805					810					815				
Trp	Cys	Val	Gln	Ile	Ala	Lys	Gly	Met	Asn	Tyr	Leu	Glu	Asp	Arg	Arg			
			820					825					830					
Leu	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Val	Leu	Val	Lys	Thr	Pro			
		835					840					845						
Gln	His	Val	Lys	Ile	Thr	Asp	Phe	Gly	Leu	Ala	Lys	Leu	Leu	Gly	Ala			
	850					855					860							
Glu	Glu	Lys	Glu	Tyr	His	Ala	Glu	Gly	Gly	Lys	Val	Pro	Ile	Lys	Trp			
865					870					875		</						

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```

          965          970          975
Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro Ser Pro
          980          985          990
Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp Met Asp
          995          1000          1005
Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln Gly Phe Phe
          1010          1015          1020
Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu Ser Ser Leu Ser Ala
          1025          1030          1035          1040
Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp Arg Asn Gly Leu Gln
          1045          1050          1055
Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln Arg Tyr Ser Ser Asp
          1060          1065          1070
Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp Asp Thr Phe Leu Pro
          1075          1080          1085
Val Pro Glu Tyr Ile Asn Gln Ser Val Pro Lys Arg Pro Ala Gly Ser
          1090          1095          1100
Val Gln Asn Pro Val Tyr His Asn Gln Pro Leu Asn Pro Ala Pro Ser
          1105          1110          1115          1120
Arg Asp Pro His Tyr Gln Asp Pro His Ser Thr Ala Val Gly Asn Pro
          1125          1130          1135
Glu Tyr Leu Asn Thr Val Gln Pro Thr Cys Val Asn Ser Thr Phe Asp
          1140          1145          1150
Ser Pro Ala His Trp Ala Gln Lys Gly Ser His Gln Ile Ser Leu Asp
          1155          1160          1165
Asn Pro Asp Tyr Gln Gln Asp Phe Phe Pro Lys Glu Ala Lys Pro Asn
          1170          1175          1180
Gly Ile Phe Lys Gly Ser Thr Ala Glu Asn Ala Glu Tyr Leu Arg Val
          1185          1190          1195          1200
Ala Pro Gln Ser Ser Glu Phe Ile Gly Ala
          1205          1210

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<210> 289  
 <211> 976  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 160  
 <223> Xaa = A or V

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<400> 289
Met Glu Arg Arg Trp Pro Leu Gly Leu Gly Leu Val Leu Leu Leu Cys
  1          5          10          15
Ala Pro Leu Pro Pro Gly Ala Arg Ala Lys Glu Val Thr Leu Met Asp
          20          25          30
Thr Ser Lys Ala Gln Gly Glu Leu Gly Trp Leu Leu Asp Pro Pro Lys
          35          40          45
Asp Gly Trp Ser Glu Gln Gln Ile Leu Asn Gly Thr Pro Leu Tyr
          50          55          60
Met Tyr Gln Asp Cys Pro Met Gln Gly Arg Arg Asp Thr Asp His Trp
          65          70          75          80
Leu Arg Ser Asn Trp Ile Tyr Arg Gly Glu Glu Ala Ser Arg Val His
          85          90          95

```

Val	Glu	Leu	Gln	Phe	Thr	Val	Arg	Asp	Cys	Lys	Ser	Phe	Pro	Gly	Gly
			100					105					110		
Ala	Gly	Pro	Leu	Gly	Cys	Lys	Glu	Thr	Phe	Asn	Leu	Leu	Tyr	Met	Glu
		115					120					125			
Ser	Asp	Gln	Asp	Val	Gly	Ile	Gln	Leu	Arg	Arg	Pro	Leu	Phe	Gln	Lys
		130				135					140				
Val	Thr	Thr	Val	Ala	Ala	Asp	Gln	Ser	Phe	Thr	Ile	Arg	Asp	Leu	Xaa
145					150					155					160
Ser	Gly	Ser	Val	Lys	Leu	Asn	Val	Glu	Arg	Cys	Ser	Leu	Gly	Arg	Leu
				165					170					175	
Thr	Arg	Arg	Gly	Leu	Tyr	Leu	Ala	Phe	His	Asn	Pro	Gly	Ala	Cys	Val
			180					185					190		
Ala	Leu	Val	Ser	Val	Arg	Val	Phe	Tyr	Gln	Arg	Cys	Pro	Glu	Thr	Leu
		195					200					205			
Asn	Gly	Leu	Ala	Gln	Phe	Pro	Asp	Thr	Leu	Pro	Gly	Pro	Ala	Gly	Leu
		210				215					220				
Val	Glu	Val	Ala	Gly	Thr	Cys	Leu	Pro	His	Ala	Arg	Ala	Ser	Pro	Arg
225					230					235					240
Pro	Ser	Gly	Ala	Pro	Arg	Met	His	Cys	Ser	Pro	Asp	Gly	Glu	Trp	Leu
				245					250					255	
Val	Pro	Val	Gly	Arg	Cys	His	Cys	Glu	Pro	Gly	Tyr	Glu	Glu	Gly	Gly
			260					265					270		
Ser	Gly	Glu	Ala	Cys	Val	Ala	Cys	Pro	Ser	Gly	Ser	Tyr	Arg	Met	Asp
		275					280					285			
Met	Asp	Thr	Pro	His	Cys	Leu	Thr	Cys	Pro	Gln	Gln	Ser	Thr	Ala	Glu
						295					300				
Ser	Glu	Gly	Ala	Thr	Ile	Cys	Thr	Cys	Glu	Ser	Gly	His	Tyr	Arg	Ala
305					310					315					320
Pro	Gly	Glu	Gly	Pro	Gln	Val	Ala	Cys	Thr	Gly	Pro	Pro	Ser	Ala	Pro
				325					330					335	
Arg	Asn	Leu	Ser	Phe	Ser	Ala	Ser	Gly	Thr	Gln	Leu	Ser	Leu	Arg	Trp
			340					345					350		
Glu	Pro	Pro	Ala	Asp	Thr	Gly	Gly	Arg	Gln	Asp	Val	Arg	Tyr	Ser	Val
		355					360					365			
Arg	Cys	Ser	Gln	Cys	Gln	Gly	Thr	Ala	Gln	Asp	Gly	Gly	Pro	Cys	Gln
		370				375					380				
Pro	Cys	Gly	Val	Gly	Val	His	Phe	Ser	Pro	Gly	Ala	Arg	Gly	Leu	Thr
385					390					395					400
Thr	Pro	Ala	Val	His	Val	Asn	Gly	Leu	Glu	Pro	Tyr	Ala	Asn	Tyr	Thr
				405					410					415	
Phe	Asn	Val	Glu	Ala	Gln	Asn	Gly	Val	Ser	Gly	Leu	Gly	Ser	Ser	Gly
			420					425					430		
His	Ala	Ser	Thr	Ser	Val	Ser	Ile	Ser	Met	Gly	His	Ala	Glu	Ser	Leu
		435					440					445			
Ser	Gly	Leu	Ser	Leu	Arg	Leu									

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Gly	Gly	Glu	Ile	Val	Ala	Val	Ile	Phe	Gly	Leu	Leu	Leu	Gly	Ala	Ala
545					550					555					560
Leu	Leu	Leu	Gly	Ile	Leu	Val	Phe	Arg	Ser	Arg	Arg	Ala	Gln	Arg	Gln
			565						570					575	
Arg	Gln	Gln	Arg	Gln	Arg	Asp	Arg	Ala	Thr	Asp	Val	Asp	Arg	Glu	Asp
			580					585					590		
Lys	Leu	Trp	Leu	Lys	Pro	Tyr	Val	Asp	Leu	Gln	Ala	Tyr	Glu	Asp	Pro
		595					600					605			
Ala	Gln	Gly	Ala	Leu	Asp	Phe	Thr	Arg	Glu	Leu	Asp	Pro	Ala	Trp	Leu
		610				615					620				
Met	Val	Asp	Thr	Val	Ile	Gly	Glu	Gly	Glu	Phe	Gly	Glu	Val	Tyr	Arg
625					630					635					640
Gly	Thr	Leu	Arg	Leu	Pro	Ser	Gln	Asp	Cys	Lys	Thr	Val	Ala	Ile	Lys
			645						650					655	
Thr	Leu	Lys	Asp	Thr	Ser	Pro	Gly	Gly	Gln	Trp	Trp	Asn	Phe	Leu	Arg
			660					665					670		
Glu	Ala	Thr	Ile	Met	Gly	Gln	Phe	Ser	His	Pro	His	Ile	Leu	His	Leu
		675					680					685			
Glu	Gly	Val	Val	Thr	Lys	Arg	Lys	Pro	Ile	Met	Ile	Ile	Thr	Glu	Phe
		690				695					700				
Met	Glu	Asn	Gly	Ala	Leu	Asp	Ala	Phe	Leu	Arg	Glu	Arg	Glu	Asp	Gln
705					710					715					720
Leu	Val	Pro	Gly	Gln	Leu	Val	Ala	Met	Leu	Gln	Gly	Ile	Ala	Ser	Gly
			725						730					735	
Met	Asn	Tyr	Leu	Ser	Asn	His	Asn	Tyr	Val	His	Arg	Asp	Leu	Ala	Ala
		740						745					750		
Arg	Asn	Ile	Leu	Val	Asn	Gln	Asn	Leu	Cys	Cys	Lys	Val	Ser	Asp	Phe
		755					760					765			
Gly	Leu	Thr	Arg	Leu	Leu	Asp	Phe	Asp	Gly	Thr	Tyr	Glu	Thr	Gln	
	770					775				780					
Gly	Gly	Lys	Ile	Pro	Ile	Arg	Trp	Thr	Ala	Pro	Glu	Ala	Ile	Ala	His
785					790					795					800
Arg	Ile	Phe	Thr	Thr	Ala	Ser	Asp	Val	Trp	Ser	Phe	Gly	Ile	Val	Met
			805						810					815	
Trp	Glu	Val	Leu	Ser	Phe	Gly	Asp	Lys	Pro	Tyr	Gly	Glu	Met	Ser	Asn
		820						825					830		
Gln	Glu	Val	Met	Lys	Ser	Ile	Glu	Asp	Gly	Tyr	Arg	Leu	Pro	Pro	Pro
		835					840					845			
Val	Asp	Cys	Pro	Ala	Pro	Leu	Tyr	Glu	Leu	Met	Lys	Asn	Cys	Trp	Ala
	850					855					860				
Tyr	Asp	Arg	Ala	Arg	Arg	Pro	His	Phe	Gln	Lys	Leu	Gln	Ala	His	Leu
865					870					875					880
Glu	Gln	Leu	Leu	Ala	Asn	Pro	His	Ser	Leu	Arg	Thr	Ile	Ala	Asn	Phe
			885						890					895	
Asp	Pro	Arg	Met	Thr	Leu	Arg	Leu	Pro	Ser	Leu	Ser	Gly	Ser	Asp	Gly
			900					905					910		
Ile	Pro	Tyr	Arg	Thr	Val	Ser	Glu	Trp	Leu	Glu	Ser	Ile	Arg	Met	Lys
		915					920					925			
Arg	Tyr	Ile	Leu	His	Phe	His	Ser	Ala	Gly	Leu	Asp	Thr	Met	Glu	Cys
	930					935					940				
Val	Leu	Glu	Leu	Thr	Ala	Glu	Asp	Leu	Thr	Gln	Met	Gly	Ile	Thr	Leu
945					950					955					960
Pro	Gly	His	Gln	Lys	Arg	Ile	Leu	Cys	Ser	Ile	Gln	Gly	Phe	Lys	Asp
			965						970					975	

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<210> 290  
 <211> 976  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 94  
 <223> Xaa = I or N

<220>  
 <221> VARIANT  
 <222> 96  
 <223> Xaa = I or F

<220>  
 <221> VARIANT  
 <222> 99  
 <223> Xaa = K or N

<220>  
 <221> VARIANT  
 <222> 350  
 <223> Xaa = P or T

<220>  
 <221> VARIANT  
 <222> 825  
 <223> Xaa = E or K

<400> 290  
 Met Glu Leu Gln Ala Ala Arg Ala Cys Phe Ala Leu Leu Trp Gly Cys  
   1                  5                  10                  15  
 Ala Leu Ala Ala Ala Ala Ala Gln Gly Lys Glu Val Val Leu Leu  
                   20                  25                  30  
 Asp Phe Ala Ala Ala Gly Gly Glu Leu Gly Trp Leu Thr His Pro Tyr  
           35                  40                  45  
 Gly Lys Gly Trp Asp Leu Met Gln Asn Ile Met Asn Asp Met Pro Ile  
   50                  55                  60  
 Tyr Met Tyr Ser Val Cys Asn Val Met Ser Gly Asp Gln Asp Asn Trp  
 65                  70                  75                  80  
 Leu Arg Thr Asn Trp Val Tyr Arg Gly Glu Ala Glu Arg Xaa Phe Xaa  
                   85                  90                  95  
 Glu Leu Xaa Phe Thr Val Arg Asp Cys Asn Ser Phe Pro Gly Gly Ala  
           100                  105                  110  
 Ser Ser Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Ala Glu Ser Asp Leu  
           115                  120                  125  
 Asp Tyr Gly Thr Asn Phe Gln Lys Arg Leu Phe Thr Lys Ile Asp Thr  
   130                  135                  140  
 Ile Ala Pro Asp Glu Ile Thr Val Ser Ser Asp Phe Glu Ala Arg His  
 145                  150                  155                  160  
 Val Lys Leu Asn Val Glu Glu Arg Ser Val Gly Pro Leu Thr Arg Lys  
                   165                  170                  175  
 Gly Phe Tyr Leu Ala Phe Gln Asp Ile Gly Ala Cys Val Ala Leu Leu  
           180                  185                  190  
 Ser Val Arg Val Tyr Tyr Lys Lys Cys Pro Glu Leu Leu Gln Gly Leu



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	195		200		205
Ala	His	Phe	Pro	Glu	Thr
210					Ile
Thr	Val	Ala	Gly	Thr	Cys
225					Val
Glu	Glu	Pro	Arg	Met	His
					Cys
					Ala
					Val
					Asp
					Gly
					Glu
					Trp
					Leu
					Val
					Pro
					Gly
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					Gly
					Ala
					Ala
					Val
					Val
					Pro

				645					650					655		
Arg	Val	Asp	Phe	Leu	Gly	Glu	Ala	Gly	Ile	Met	Gly	Gln	Phe	Ser	His	
			660					665					670			
His	Asn	Ile	Ile	Arg	Leu	Glu	Gly	Val	Ile	Ser	Lys	Tyr	Lys	Pro	Met	
			675				680					685				
Met	Ile	Ile	Thr	Glu	Tyr	Met	Glu	Asn	Gly	Ala	Leu	Asp	Lys	Phe	Leu	
			690			695					700					
Arg	Glu	Lys	Asp	Gly	Glu	Phe	Ser	Val	Leu	Gln	Leu	Val	Gly	Met	Leu	
705					710					715					720	
Arg	Gly	Ile	Ala	Ala	Gly	Met	Lys	Tyr	Leu	Ala	Asn	Met	Asn	Tyr	Val	
			725						730					735		
His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Val	Asn	Ser	Asn	Leu	Val	
			740					745					750			
Cys	Lys	Val	Ser	Asp	Phe	Gly	Leu	Ser	Arg	Val	Leu	Glu	Asp	Asp	Pro	
			755				760					765				
Glu	Ala	Thr	Tyr	Thr	Thr	Ser	Gly	Gly	Lys	Ile	Pro	Ile	Arg	Trp	Thr	
			770			775						780				
Ala	Pro	Glu	Ala	Ile	Ser	Tyr	Arg	Lys	Phe	Thr	Ser	Ala	Ser	Asp	Val	
785					790					795					800	
Trp	Ser	Phe	Gly	Ile	Val	Met	Trp	Glu	Val	Met	Thr	Tyr	Gly	Glu	Arg	
			805						810					815		
Pro	Tyr	Trp	Glu	Leu	Ser	Asn	His	Xaa	Val	Met	Lys	Ala	Ile	Asn	Asp	
			820					825					830			
Gly	Phe	Arg	Leu	Pro	Thr	Pro	Met	Asp	Cys	Pro	Ser	Ala	Ile	Tyr	Gln	
			835				840					845				
Leu	Met	Met	Gln	Cys	Trp	Gln	Gln	Glu	Arg	Ala	Arg	Arg	Pro	Lys	Phe	
			850			855						860				
Ala	Asp	Ile	Val	Ser	Ile	Leu	Asp	Lys	Leu	Ile	Arg	Ala	Pro	Asp	Ser	
865					870					875					880	
Leu	Lys	Thr	Leu	Ala	Asp	Phe	Asp	Pro	Arg	Val	Ser	Ile	Arg	Leu	Pro	
			885											895		
Ser	Thr	Ser	Gly	Ser	Glu	Gly	Val	Pro	Phe	Arg	Thr	Val	Ser	Glu	Trp	
			900					905					910			
Leu	Glu	Ser	Ile	Lys	Met	Gln	Gln	Tyr	Thr	Glu	His	Phe	Met	Ala	Ala	
			915				920					925				
Gly	Tyr	Thr	Ala	Ile	Glu	Lys	Val	Val	Gln	Met	Thr	Asn	Asp	Asp	Ile	
			930			935						940				
Lys	Arg	Ile	Gly	Val	Arg	Leu	Pro	Gly	His	Gln	Lys	Arg	Ile	Ala	Tyr	
945					950					955					960	
Ser	Leu	Leu	Gly	Leu	Lys	Asp	Gln	Val	Asn	Thr	Val	Gly	Ile	Pro	Ile	
			965						970					975		

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<220>  
<221> VARIANT  
<222> 914  
<223> Xaa = R or H
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<400> 291
Met Asp Cys Gln Leu Ser Ile Leu Leu Leu Leu Ser Cys Ser Val Leu
 1             5             10             15
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Asp Ser Phe Gly Glu Leu Ile Pro Gln Pro Ser Asn Glu Val Asn Leu
      20      25      30
Leu Asp Ser Lys Thr Ile Gln Gly Glu Leu Gly Trp Ile Ser Tyr Pro
      35      40      45
Ser His Gly Trp Glu Glu Ile Ser Gly Val Asp Glu His Tyr Thr Pro
      50      55      60
Ile Arg Thr Tyr Gln Val Cys Asn Val Met Asp His Ser Gln Asn Asn
      65      70      75      80
Trp Leu Arg Thr Asn Trp Val Pro Arg Asn Ser Ala Gln Lys Ile Tyr
      85      90      95
Val Glu Leu Lys Phe Thr Leu Arg Asp Cys Asn Ser Ile Pro Leu Val
      100      105      110
Leu Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Met Glu Ser Asp
      115      120      125
Asp Asp His Gly Val Lys Phe Arg Glu His Gln Phe Thr Lys Ile Asp
      130      135      140
Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Met Asp Leu Gly Asp Arg
      145      150      155      160
Ile Leu Lys Leu Asn Thr Glu Ile Arg Glu Val Gly Pro Val Asn Lys
      165      170      175
Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys Val Ala Leu
      180      185      190
Val Ser Val Arg Val Tyr Phe Lys Lys Cys Pro Phe Thr Val Lys Asn
      195      200      205
Leu Ala Met Phe Pro Asp Thr Val Pro Met Asp Ser Gln Ser Leu Val
      210      215      220
Glu Val Arg Gly Ser Cys Val Asn Asn Ser Lys Glu Glu Asp Pro Pro
      225      230      235      240
Arg Met Tyr Cys Ser Thr Glu Gly Glu Trp Leu Val Pro Ile Gly Lys
      245      250      255
Cys Ser Cys Asn Ala Gly Tyr Glu Glu Arg Gly Phe Met Cys Gln Ala
      260      265      270
Cys Arg Pro Gly Phe Tyr Lys Ala Leu Asp Gly Asn Met Lys Cys Ala
      275      280      285
Lys Cys Pro Pro His Ser Ser Thr Gln Glu Asp Gly Ser Met Asn Cys
      290      295      300
Arg Cys Glu Asn Asn Tyr Phe Arg Ala Asp Lys Asp Pro Pro Ser Met
      305      310      315      320
Ala Cys Thr Arg Pro Pro Ser Ser Pro Arg Asn Val Ile Ser Asn Ile
      325      330      335
Asn Glu Thr Ser Val Ile Leu Asp Trp Ser Trp Pro Leu Asp Thr Gly
      340      345      350
Gly Arg Lys Asp Val Thr Phe Asn Ile Ile Cys Lys Lys Cys Gly Trp
      355      360      365
Asn Ile Lys Gln Cys Glu Pro Cys Ser Pro Asn Val Arg Phe Leu Pro
      370      375      380
Arg Gln Phe Gly Leu Thr Asn Thr Thr Val Thr Val Thr Asp Leu Leu
      385      390      395      400
Ala His Thr Asn Tyr Thr Phe Glu Ile Asp Ala Val Asn Gly Val Ser
      405      410      415
Glu Leu Ser Ser Pro Pro Arg Gln Phe Ala Ala Val Ser Ile Thr Thr
      420      425      430
Asn Gln Ala Ala Pro Ser Pro Val Leu Thr Ile Lys Lys Asp Arg Thr
      435      440      445
Ser Arg Asn Ser Ile Ser Leu Ser Trp Gln Glu Pro Glu His Pro Asn
      450      455      460

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Gly Ile Ile Leu Asp Tyr Glu Val Lys Tyr Tyr Glu Lys Gln Glu Gln  
 465 470 475 480  
 Glu Thr Ser Tyr Thr Ile Leu Arg Ala Arg Gly Thr Asn Val Thr Ile  
 485 490 495  
 Ser Ser Leu Lys Pro Asp Thr Ile Tyr Val Phe Gln Ile Arg Ala Arg  
 500 505 510  
 Thr Ala Ala Gly Tyr Gly Thr Asn Ser Arg Lys Phe Glu Phe Glu Thr  
 515 520 525  
 Ser Pro Asp Ser Phe Ser Ile Ser Gly Glu Ser Ser Gln Val Val Met  
 530 535 540  
 Ile Ala Ile Ser Ala Ala Val Ala Ile Ile Leu Leu Thr Val Val Ile  
 545 550 555 560  
 Tyr Val Leu Ile Gly Arg Phe Cys Gly Tyr Lys Ser Lys His Gly Ala  
 565 570 575  
 Asp Glu Lys Arg Leu His Phe Gly Asn Gly His Leu Lys Leu Pro Gly  
 580 585 590  
 Leu Arg Thr Tyr Val Asp Pro His Thr Tyr Glu Asp Pro Thr Gln Ala  
 595 600 605  
 Val His Glu Phe Ala Lys Glu Leu Asp Ala Thr Asn Ile Ser Ile Asp  
 610 615 620  
 Lys Val Val Gly Ala Gly Glu Phe Gly Glu Val Cys Ser Gly Arg Leu  
 625 630 635 640  
 Lys Leu Pro Ser Lys Lys Glu Ile Ser Val Ala Ile Lys Thr Leu Lys  
 645 650 655  
 Val Gly Tyr Thr Glu Lys Gln Arg Arg Asp Phe Leu Gly Glu Ala Ser  
 660 665 670  
 Ile Met Gly Gln Phe Asp His Pro Asn Ile Ile Arg Leu Glu Gly Val  
 675 680 685  
 Val Thr Lys Ser Lys Pro Val Met Ile Val Thr Glu Tyr Met Glu Asn  
 690 695 700  
 Gly Ser Leu Asp Ser Phe Leu Arg Lys His Asp Ala Gln Phe Thr Val  
 705 710 715 720  
 Ile Gln Leu Val Gly Met Leu Arg Gly Ile Ala Ser Gly Met Lys Tyr  
 725 730 735  
 Leu Ser Asp Met Gly Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile  
 740 745 750  
 Leu Ile Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser  
 755 760 765  
 Arg Val Leu Glu Asp Asp Pro Glu Ala Ala Tyr Thr Thr Arg Gly Gly  
 770 775 780  
 Lys Ile Pro Ile Arg Trp Thr Ser Pro Glu Ala Ile Ala Tyr Arg Lys  
 785 790 795 800  
 Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Leu Trp Glu  
 805 810 815  
 Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Glu Met Ser Asn Gln Asp  
 820 825 830  
 Val Ile Lys Ala Val Asp Glu Gly Tyr Arg Leu Pro Pro Met Asp  
 835 840 845  
 Cys Pro Ala Ala Leu Tyr Gln Leu Met Leu Asp Cys Trp Gln Lys Asp  
 850 855 860  
 Arg Asn Asn Arg Pro Lys Phe Glu Gln Ile Val Ser Ile Leu Asp Lys  
 865 870 875 880  
 Leu Ile Arg Asn Pro Gly Ser Leu Lys Ile Ile Thr Ser Ala Ala Ala  
 885 890 895  
 Arg Pro Ser Asn Leu Leu Leu Asp Gln Ser Asn Val Asp Ile Thr Thr  
 900 905 910

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```

Phe Xaa Thr Thr Gly Asp Trp Leu Asn Gly Val Trp Thr Ala His Cys
      915      920      925
Lys Glu Ile Phe Thr Gly Val Glu Tyr Ser Ser Cys Asp Thr Ile Ala
      930      935      940
Lys Ile Ser Thr Asp Asp Met Lys Lys Val Gly Val Thr Val Val Gly
945      950      955      960
Pro Gln Lys Lys Ile Ile Ser Ser Ile Lys Ala Leu Glu Thr Gln Ser
      965      970      975
Lys Asn Gly Pro Val Pro Val
      980

```

```

<210> 292
<211> 998
<212> PRT
<213> Homo sapiens

```

```

<220>
<221> VARIANT
<222> 138
<223> Xaa = I or V

```

```

<220>
<221> VARIANT
<222> 278
<223> Xaa = P or S

```

```

<400> 292
Met Val Phe Gln Thr Arg Tyr Pro Ser Trp Ile Ile Leu Cys Tyr Ile
 1      5      10      15
Trp Leu Leu Arg Phe Ala His Thr Gly Glu Ala Gln Ala Ala Lys Glu
      20      25      30
Val Leu Leu Leu Asp Ser Lys Ala Gln Gln Thr Glu Leu Glu Trp Ile
      35      40      45
Ser Ser Pro Pro Asn Gly Trp Glu Glu Ile Ser Gly Leu Asp Glu Asn
      50      55      60
Tyr Thr Pro Ile Arg Thr Tyr Gln Val Cys Gln Val Met Glu Pro Asn
      65      70      75      80
Gln Asn Asn Trp Leu Arg Thr Asn Trp Ile Ser Lys Gly Asn Ala Gln
      85      90      95
Arg Ile Phe Val Glu Leu Lys Phe Thr Leu Arg Asp Cys Asn Ser Leu
      100      105      110
Pro Gly Val Leu Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Tyr
      115      120      125
Glu Thr Asp Tyr Asp Thr Gly Arg Asn Xaa Arg Glu Asn Leu Tyr Val
      130      135      140
Lys Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Gly Asp Leu
      145      150      155      160
Gly Glu Arg Lys Met Lys Leu Asn Thr Glu Val Arg Glu Ile Gly Pro
      165      170      175
Leu Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys
      180      185      190
Ile Ala Leu Val Ser Val Lys Val Tyr Tyr Lys Lys Cys Trp Ser Ile
      195      200      205
Ile Glu Asn Leu Ala Ile Phe Pro Asp Thr Val Thr Gly Ser Glu Phe
      210      215      220

```

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Ser Ser Leu Val Glu Val Arg Gly Thr Cys Val Ser Ser Ala Glu Glu  
 225 230 235 240  
 Glu Ala Glu Asn Ala Pro Arg Met His Cys Ser Ala Glu Gly Glu Trp  
 245 250 255  
 Leu Val Pro Ile Gly Lys Cys Ile Cys Lys Ala Gly Tyr Gln Gln Lys  
 260 265 270  
 Gly Asp Thr Cys Glu Xaa Cys Gly Arg Gly Phe Tyr Lys Ser Ser Ser  
 275 280 285  
 Gln Asp Leu Gln Cys Ser Arg Cys Pro Thr His Ser Phe Ser Asp Lys  
 290 295 300  
 Glu Gly Ser Ser Arg Cys Glu Cys Glu Asp Gly Tyr Tyr Arg Ala Pro  
 305 310 315 320  
 Ser Asp Pro Pro Tyr Val Ala Cys Thr Arg Pro Pro Ser Ala Pro Gln  
 325 330 335  
 Asn Leu Ile Phe Asn Ile Asn Gln Thr Thr Val Ser Leu Glu Trp Ser  
 340 345 350  
 Pro Pro Ala Asp Asn Gly Gly Arg Asn Asp Val Thr Tyr Arg Ile Leu  
 355 360 365  
 Cys Lys Arg Cys Ser Trp Glu Gln Gly Glu Cys Val Pro Cys Gly Ser  
 370 375 380  
 Asn Ile Gly Tyr Met Pro Gln Gln Thr Gly Leu Glu Asp Asn Tyr Val  
 385 390 395 400  
 Thr Val Met Asp Leu Leu Ala His Ala Asn Tyr Thr Phe Glu Val Glu  
 405 410 415  
 Ala Val Asn Gly Val Ser Asp Leu Ser Arg Ser Gln Arg Leu Phe Ala  
 420 425 430  
 Ala Val Ser Ile Thr Thr Gly Gln Ala Ala Pro Ser Gln Val Ser Gly  
 435 440 445  
 Val Met Lys Glu Arg Val Leu Gln Arg Ser Val Glu Leu Ser Trp Gln  
 450 455 460  
 Glu Pro Glu His Pro Asn Gly Val Ile Thr Glu Tyr Glu Ile Lys Tyr  
 465 470 475 480  
 Tyr Glu Lys Asp Gln Arg Glu Arg Thr Tyr Ser Thr Val Lys Thr Lys  
 485 490 495  
 Ser Thr Ser Ala Ser Ile Asn Asn Leu Lys Pro Gly Thr Val Tyr Val  
 500 505 510  
 Phe Gln Ile Arg Ala Phe Thr Ala Ala Gly Tyr Gly Asn Tyr Ser Pro  
 515 520 525  
 Arg Leu Asp Val Ala Thr Leu Glu Glu Ala Thr Gly Lys Met Phe Glu  
 530 535 540  
 Ala Thr Ala Val Ser Ser Glu Gln Asn Pro Val Ile Ile Ile Ala Val  
 545 550 555 560  
 Val Ala Val Ala Gly Thr Ile Ile Leu Val Phe Met Val Phe Gly Phe  
 565 570 575  
 Ile Ile Gly Arg Arg His Cys Gly Tyr Ser Lys Ala Asp Gln Glu Gly  
 580 585 590  
 Asp Glu Glu Leu Tyr Phe His Phe Lys Phe Pro Gly Thr Lys Thr Tyr  
 595 600 605  
 Ile Asp Pro Glu Thr Tyr Glu Asp Pro Asn Arg Ala Val His Gln Phe  
 610 615 620  
 Ala Lys Glu Leu Asp Ala Ser Cys Ile Lys Ile Glu Arg Val Ile Gly  
 625 630 635 640  
 Ala Gly Glu Phe Gly Glu Val Cys Ser Gly Arg Leu Lys Leu Pro Gly  
 645 650 655  
 Lys Arg Asp Val Ala Val Ala Ile Lys Thr Leu Lys Val Gly Tyr Thr  
 660 665 670

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Glu Lys Gln Arg Arg Asp Phe Leu Cys Glu Ala Ser Ile Met Gly Gln  
           675                  680                  685  
 Phe Asp His Pro Asn Val Val His Leu Glu Gly Val Val Thr Arg Gly  
           690                  695                  700  
 Lys Pro Val Met Ile Val Ile Glu Phe Met Glu Asn Gly Ala Leu Asp  
 705                  710                  715                  720  
 Ala Phe Leu Arg Lys His Asp Gly Gln Phe Thr Val Ile Gln Leu Val  
                   725                  730                  735  
 Gly Met Leu Arg Gly Ile Ala Ala Gly Met Arg Tyr Leu Ala Asp Met  
                   740                  745                  750  
 Gly Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser  
                   755                  760                  765  
 Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val Ile Glu  
                   770                  775                  780  
 Asp Asp Pro Glu Ala Val Tyr Thr Thr Thr Gly Gly Lys Ile Pro Val  
 785                  790                  795                  800  
 Arg Trp Thr Ala Pro Glu Ala Ile Gln Tyr Arg Lys Phe Thr Ser Ala  
                   805                  810                  815  
 Ser Asp Val Trp Ser Tyr Gly Ile Val Met Trp Glu Val Met Ser Tyr  
                   820                  825                  830  
 Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp Val Ile Lys Ala  
                   835                  840                  845  
 Ile Glu Glu Gly Tyr Arg Leu Pro Ala Pro Met Asp Cys Pro Ala Gly  
                   850                  855                  860  
 Leu His Gln Leu Met Leu Asp Cys Trp Gln Lys Glu Arg Ala Glu Arg  
 865                  870                  875                  880  
 Pro Lys Phe Glu Gln Ile Val Gly Ile Leu Asp Lys Met Ile Arg Asn  
                   885                  890                  895  
 Pro Asn Ser Leu Lys Thr Pro Leu Gly Thr Cys Ser Arg Pro Ile Ser  
                   900                  905                  910  
 Pro Leu Leu Asp Gln Asn Thr Pro Asp Phe Thr Thr Phe Cys Ser Val  
                   915                  920                  925  
 Gly Glu Trp Leu Gln Ala Ile Lys Met Glu Arg Tyr Lys Asp Asn Phe  
 930                  935                  940  
 Thr Ala Ala Gly Tyr Asn Ser Leu Glu Ser Val Ala Arg Met Thr Ile  
 945                  950                  955                  960  
 Glu Asp Val Met Ser Leu Gly Ile Thr Leu Val Gly His Gln Lys Lys  
                   965                  970                  975  
 Ile Met Ser Ser Ile Gln Thr Met Arg Ala Gln Met Leu His Leu His  
                   980                  985                  990  
 Gly Thr Gly Ile Gln Val  
                   995

<210> 293  
 <211> 1005  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 301  
 <223> Xaa = A or V

<220>  
 <221> VARIANT

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&lt;222&gt; 444

&lt;223&gt; Xaa = V or M

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 612

&lt;223&gt; Xaa = E or Q

&lt;400&gt; 293

```

Met Ala Pro Ala Arg Gly Arg Leu Pro Pro Ala Leu Trp Val Val Thr
 1           5           10           15
Ala Ala Ala Ala Ala Thr Cys Val Ser Ala Ala Arg Gly Glu Val
      20           25           30
Asn Leu Leu Asp Thr Ser Thr Ile His Gly Asp Trp Gly Trp Leu Thr
      35           40           45
Tyr Pro Ala His Gly Trp Asp Ser Ile Asn Glu Val Asp Glu Ser Phe
      50           55           60
Gln Pro Ile His Thr Tyr Gln Val Cys Asn Val Met Ser Pro Asn Gln
      65           70           75           80
Asn Asn Trp Leu Arg Thr Ser Trp Val Pro Arg Asp Gly Ala Arg Arg
      85           90           95
Val Tyr Ala Glu Ile Lys Phe Thr Leu Arg Asp Cys Asn Ser Met Pro
      100          105          110
Gly Val Leu Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Leu Glu
      115          120          125
Ser Asp Arg Asp Leu Gly Ala Ser Thr Gln Glu Ser Gln Phe Leu Lys
      130          135          140
Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr Gly Ala Asp Leu Gly
      145          150          155          160
Val Arg Arg Leu Lys Leu Asn Thr Glu Val Arg Ser Val Gly Pro Leu
      165          170          175
Ser Lys Arg Gly Phe Tyr Leu Ala Phe Gln Asp Ile Gly Ala Cys Leu
      180          185          190
Ala Ile Leu Ser Leu Arg Ile Tyr Tyr Lys Lys Cys Pro Ala Met Val
      195          200          205
Arg Asn Leu Ala Ala Phe Ser Glu Ala Val Thr Gly Ala Asp Ser Ser
      210          215          220
Ser Leu Val Glu Val Arg Gly Gln Cys Val Arg His Ser Glu Glu Arg
      225          230          235          240
Asp Thr Pro Lys Met Tyr Cys Ser Ala Glu Gly Glu Trp Leu Val Pro
      245          250          255
Ile Gly Lys Cys Val Cys Ser Ala Gly Tyr Glu Glu Arg Arg Asp Ala
      260          265          270
Cys Val Ala Cys Glu Leu Gly Phe Tyr Lys Ser Ala Pro Gly Asp Gln
      275          280          285
Leu Cys Ala Arg Cys Pro Pro His Ser His Ser Ala Xaa Pro Ala Ala
      290          295          300
Gln Ala Cys His Cys Asp Leu Ser Tyr Tyr Arg Ala Ala Leu Asp Pro
      305          310          315          320
Pro Ser Ser Ala Cys Thr Arg Pro Pro Ser Ala Pro Val Asn Leu Ile
      325          330          335
Ser Ser Val Asn Gly Thr Ser Val Thr Leu Glu Trp Ala Pro Pro Leu
      340          345          350
Asp Pro Gly Gly Arg Ser Asp Ile Thr Tyr Asn Ala Val Cys Arg Arg
      355          360          365
Cys Pro Trp Ala Leu Ser Arg Cys Glu Ala Cys Gly Ser Gly Thr Arg

```



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370		375		380
Phe Val Pro Gln Gln Thr Ser Leu Val Gln Ala Ser Leu Leu Val Ala				
385		390		395
Asn Leu Leu Ala His Met Asn Tyr Ser Phe Trp Ile Glu Ala Val Asn				
	405		410	415
Gly Val Ser Asp Leu Ser Pro Glu Pro Arg Arg Ala Ala Val Val Asn				
	420		425	430
Ile Thr Thr Asn Gln Ala Ala Pro Ser Gln Val Xaa Val Ile Arg Gln				
	435		440	445
Glu Arg Ala Gly Gln Thr Ser Val Ser Leu Leu Trp Gln Glu Pro Glu				
	450		455	460
Gln Pro Asn Gly Ile Ile Leu Glu Tyr Glu Ile Lys Tyr Tyr Glu Lys				
465		470		475
Asp Lys Glu Met Gln Ser Tyr Ser Thr Leu Lys Ala Val Thr Thr Arg				
	485		490	495
Ala Thr Val Ser Gly Leu Lys Pro Gly Thr Arg Tyr Val Phe Gln Val				
	500		505	510
Arg Ala Arg Thr Ser Ala Gly Cys Gly Arg Phe Ser Gln Ala Met Glu				
	515		520	525
Val Glu Thr Gly Lys Pro Arg Pro Arg Tyr Asp Thr Arg Thr Ile Val				
	530		535	540
Trp Ile Cys Leu Thr Leu Ile Thr Gly Leu Val Val Leu Leu Leu Leu				
545		550		555
Leu Ile Cys Lys Lys Arg His Cys Gly Tyr Ser Lys Ala Phe Gln Asp				
	565		570	575
Ser Asp Glu Glu Lys Met His Tyr Gln Asn Gly Gln Ala Pro Pro Pro				
	580		585	590
Val Phe Leu Pro Leu His His Pro Pro Gly Lys Leu Pro Glu Pro Gln				
	595		600	605
Phe Tyr Ala Xaa Pro His Thr Tyr Glu Glu Pro Gly Arg Ala Gly Arg				
	610		615	620
Ser Phe Thr Arg Glu Ile Glu Ala Ser Arg Ile His Ile Glu Lys Ile				
625		630		635
Ile Gly Ser Gly Asp Ser Gly Glu Val Cys Tyr Gly Arg Leu Arg Val				
	645		650	655
Pro Gly Gln Arg Asp Val Pro Val Ala Ile Lys Ala Leu Lys Ala Gly				
	660		665	670
Tyr Thr Glu Arg Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser Ile Met				
	675		680	685
Gly Gln Phe Asp His Pro Asn Ile Ile Arg Leu Glu Gly Val Val Thr				
	690		695	700
Arg Gly Arg Leu Ala Met Ile Val Thr Glu Tyr Met Glu Asn Gly Ser				
705		710		715
Leu Asp Thr Phe Leu Arg Thr His Asp Gly Gln Phe Thr Ile Met Gln				
	725		730	735
Leu Val Gly Met Leu Arg Gly Val Gly Ala Gly Met Arg Tyr Leu Ser				
	740		745	750
Asp Leu Gly Tyr Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val				
	755		760	765
Asp Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val				
	770		775	780
Leu Glu Asp Asp Pro Asp Ala Ala Tyr Thr Thr Gly Gly Lys Ile				
785		790		795
Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Ala Phe Arg Thr Phe Ser				
	805		810	815
Ser Ala Ser Asp Val Trp Ser Phe Gly Val Val Met Trp Glu Val Leu				

			820					825					830					
Ala	Tyr	Gly	Glu	Arg	Pro	Tyr	Trp	Asn	Met	Thr	Asn	Arg	Asp	Val	Ile			
		835					840					845						
Ser	Ser	Val	Glu	Glu	Gly	Tyr	Arg	Leu	Pro	Ala	Pro	Met	Gly	Cys	Pro			
		850				855					860							
His	Ala	Leu	His	Gln	Leu	Met	Leu	Asp	Cys	Trp	His	Lys	Asp	Arg	Ala			
865					870				875						880			
Gln	Arg	Pro	Arg	Phe	Ser	Gln	Ile	Val	Ser	Val	Leu	Asp	Ala	Leu	Ile			
				885					890						895			
Arg	Ser	Pro	Glu	Ser	Leu	Arg	Ala	Thr	Ala	Thr	Val	Ser	Arg	Cys	Pro			
			900					905					910					
Pro	Pro	Ala	Phe	Val	Arg	Ser	Cys	Phe	Asp	Leu	Arg	Gly	Gly	Ser	Gly			
		915				920					925							
Gly	Gly	Gly	Gly	Leu	Thr	Val	Gly	Asp	Trp	Leu	Asp	Ser	Ile	Arg	Met			
		930				935					940							
Gly	Arg	Tyr	Arg	Asp	His	Phe	Ala	Ala	Gly	Gly	Tyr	Ser	Ser	Leu	Gly			
945					950				955						960			
Met	Val	Leu	Arg	Met	Asn	Ala	Gln	Asp	Val	Arg	Ala	Leu	Gly	Ile	Thr			
				965					970						975			
Leu	Met	Gly	His	Gln	Lys	Lys	Ile	Leu	Gly	Ser	Ile	Gln	Thr	Met	Arg			
			980					985					990					
Ala	Gln	Leu	Thr	Ser	Thr	Gln	Gly	Pro	Arg	Arg	His	Leu						
		995				1000						1005						

```
<210> 294
<211> 984
<212> PRT
<213> Homo sapiens
```

```
<220>  
<221> VARIANT  
<222> 87  
<223> Xaa = T or S
```

```
<220>
<221> VARIANT
<222> 152, 367
<223> Xaa = G or R
```

```
<220>  
<221> VARIANT  
<222> 274  
<223> Xaa = T or R
```

```
<220>  
<221> VARIANT  
<222> 485  
<223> Xaa = R or S
```

```
<220>  
<221> VARIANT  
<222> 813  
<223> Xaa = V or I
```

**<220>**

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<221> VARIANT  
 <222> 847  
 <223> Xaa = M or T

<220>  
 <221> VARIANT  
 <222> 973  
 <223> Xaa = R or W

<400> 294  
 Met Ala Leu Asp Tyr Leu Leu Leu Leu Leu Leu Ala Ser Ala Val Ala  
 1 5 10 15  
 Ala Met Glu Glu Thr Leu Met Asp Thr Arg Thr Ala Thr Ala Glu Leu  
 20 25 30  
 Gly Trp Thr Ala Asn Pro Ala Ser Gly Trp Glu Glu Val Ser Gly Tyr  
 35 40 45  
 Asp Glu Asn Leu Asn Thr Ile Arg Thr Tyr Gln Val Cys Asn Val Phe  
 50 55 60  
 Glu Pro Asn Gln Asn Asn Trp Leu Leu Thr Thr Phe Ile Asn Arg Arg  
 65 70 75 80  
 Gly Ala His Arg Ile Tyr Xaa Glu Met Arg Phe Thr Val Arg Asp Cys  
 85 90 95  
 Ser Ser Leu Pro Asn Val Pro Gly Ser Cys Lys Glu Thr Phe Asn Leu  
 100 105 110  
 Tyr Tyr Tyr Glu Thr Asp Ser Val Ile Ala Thr Lys Lys Ser Ala Phe  
 115 120 125  
 Trp Ser Glu Ala Pro Tyr Leu Lys Val Asp Thr Ile Ala Ala Asp Glu  
 130 135 140  
 Ser Phe Ser Gln Val Asp Phe Xaa Gly Arg Leu Met Lys Val Asn Thr  
 145 150 155 160  
 Glu Val Arg Ser Phe Gly Pro Leu Thr Arg Asn Gly Phe Tyr Leu Ala  
 165 170 175  
 Phe Gln Asp Tyr Gly Ala Cys Met Ser Leu Leu Ser Val Arg Val Phe  
 180 185 190  
 Phe Lys Lys Cys Pro Ser Ile Val Gln Asn Phe Ala Val Phe Pro Glu  
 195 200 205  
 Thr Met Thr Gly Ala Glu Ser Thr Ser Leu Val Ile Ala Arg Gly Thr  
 210 215 220  
 Cys Ile Pro Asn Ala Glu Val Asp Val Pro Ile Lys Leu Tyr Cys  
 225 230 235 240  
 Asn Gly Asp Gly Glu Trp Met Val Pro Ile Gly Arg Cys Thr Cys Lys  
 245 250 255  
 Pro Gly Tyr Glu Pro Glu Asn Ser Val Ala Cys Lys Ala Cys Pro Ala  
 260 265 270  
 Gly Xaa Phe Lys Ala Ser Gln Glu Ala Glu Gly Cys Ser His Cys Pro  
 275 280 285  
 Ser Asn Ser Arg Ser Pro Ala Glu Ala Ser Pro Ile Cys Thr Cys Arg  
 290 295 300  
 Thr Gly Tyr Tyr Arg Ala Asp Phe Asp Pro Pro Glu Val Ala Cys Thr  
 305 310 315 320  
 Ser Val Pro Ser Gly Pro Arg Asn Val Ile Ser Ile Val Asn Glu Thr  
 325 330 335  
 Ser Ile Ile Leu Glu Trp His Pro Pro Arg Glu Thr Gly Gly Arg Asp  
 340 345 350  
 Asp Val Thr Tyr Asn Ile Ile Cys Lys Lys Cys Arg Ala Asp Xaa Arg  
 355 360 365

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Ser	Cys	Ser	Arg	Cys	Asp	Asp	Asn	Val	Glu	Phe	Val	Pro	Arg	Gln	Leu
370					375						380				
Gly	Leu	Thr	Glu	Cys	Arg	Val	Ser	Ile	Ser	Ser	Leu	Trp	Ala	His	Thr
385				390					395						400
Pro	Tyr	Thr	Phe	Asp	Ile	Gln	Ala	Ile	Asn	Gly	Val	Ser	Ser	Lys	Ser
			405					410						415	
Pro	Phe	Pro	Pro	Gln	His	Val	Ser	Val	Asn	Ile	Thr	Thr	Asn	Gln	Ala
		420					425						430		
Ala	Pro	Ser	Thr	Val	Pro	Ile	Met	His	Gln	Val	Ser	Ala	Thr	Met	Arg
	435					440						445			
Ser	Ile	Thr	Leu	Ser	Trp	Pro	Gln	Pro	Glu	Gln	Pro	Asn	Gly	Ile	Ile
450					455						460				
Leu	Asp	Tyr	Glu	Ile	Arg	Tyr	Tyr	Glu	Lys	Glu	His	Asn	Glu	Phe	Asn
465				470						475					480
Ser	Ser	Met	Ala	Xaa	Ser	Gln	Thr	Asn	Thr	Ala	Arg	Ile	Asp	Gly	Leu
			485						490					495	
Arg	Pro	Gly	Met	Val	Tyr	Val	Val	Gln	Val	Arg	Ala	Arg	Thr	Val	Ala
			500					505						510	
Gly	Tyr	Gly	Lys	Phe	Ser	Gly	Lys	Met	Cys	Phe	Gln	Thr	Leu	Thr	Asp
	515					520						525			
Asp	Asp	Tyr	Lys	Ser	Glu	Leu	Arg	Glu	Gln	Leu	Pro	Leu	Ile	Ala	Gly
530					535						540				
Ser	Ala	Ala	Ala	Gly	Val	Val	Phe	Val	Val	Ser	Leu	Val	Ala	Ile	Ser
545				550						555					560
Ile	Val	Cys	Ser	Arg	Lys	Arg	Ala	Tyr	Ser	Lys	Glu	Ala	Val	Tyr	Ser
			565						570					575	
Asp	Lys	Leu	Gln	His	Tyr	Ser	Thr	Gly	Arg	Gly	Ser	Pro	Gly	Met	Lys
		580						585					590		
Ile	Tyr	Ile	Asp	Pro	Phe	Thr	Tyr	Glu	Asp	Pro	Asn	Glu	Ala	Val	Arg
	595						600					605			
Glu	Phe	Ala	Lys	Glu	Ile	Asp	Val	Ser	Phe	Val	Lys	Ile	Glu	Glu	Val
	610				615						620				
Ile	Gly	Ala	Gly	Glu	Phe	Gly	Glu	Val	Tyr	Lys	Gly	Arg	Leu	Lys	Leu
625				630						635					640
Pro	Gly	Lys	Arg	Glu	Ile	Tyr	Val	Ala	Ile	Lys	Thr	Leu	Lys	Ala	Gly
			645						650					655	
Tyr	Ser	Glu	Lys	Gln	Arg	Arg	Asp	Phe	Leu	Ser	Glu	Ala	Ser	Ile	Met
		660					665						670		
Gly	Gln	Phe	Asp	His	Pro	Asn	Ile	Ile	Arg	Leu	Glu	Gly	Val	Val	Thr
	675						680						685		
Lys	Ser	Arg	Pro	Val	Met	Ile	Ile	Thr	Glu	Phe	Met	Glu	Asn	Gly	Ala
	690					695					700				
Leu	Asp	Ser	Phe	Leu	Arg	Gln	Asn	Asp	Gly	Gln	Phe	Thr	Val	Ile	Gln
705				710						715					720
Leu	Val	Gly	Met	Leu	Arg	Gly	Ile	Ala	Ala	Gly	Met	Lys	Tyr	Leu	Ala
			725						730					735	
Glu	Met	Asn	Tyr	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Val
		740						745					750		
Asn	Ser	Asn	Leu	Val	Cys	Lys	Val	Ser	Asp	Phe	Gly	Leu	Ser	Arg	Tyr
	755						760					765			
Leu	Gln	Asp	Asp	Thr	Ser	Asp	Pro	Thr	Tyr	Thr	Ser	Ser	Leu	Gly	Gly
770						775					780				
Lys	Ile	Pro	Val	Arg	Trp	Thr	Ala	Pro	Glu	Ala	Ile	Ala	Tyr	Arg	Lys
785				790						795					800
Phe	Thr	Ser	Ala	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Ile	Xaa	Met	Trp	Glu
			805						810					815	

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```

Val Met Ser Phe Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp
      820      825      830
Val Ile Asn Ala Ile Glu Gln Asp Tyr Arg Leu Pro Pro Xaa Asp
      835      840      845
Cys Pro Ala Ala Leu His Gln Leu Met Leu Asp Cys Trp Gln Lys Asp
      850      855      860
Arg Asn Ser Arg Pro Arg Phe Ala Glu Ile Val Asn Thr Leu Asp Lys
865      870      875      880
Met Ile Arg Asn Pro Ala Ser Leu Lys Thr Val Ala Thr Ile Thr Ala
      885      890      895
Val Pro Ser Gln Pro Leu Leu Asp Arg Ser Ile Pro Asp Phe Thr Ala
      900      905      910
Phe Thr Thr Val Asp Asp Trp Leu Ser Ala Ile Lys Met Val Gln Tyr
      915      920      925
Arg Asp Ser Phe Leu Thr Ala Gly Phe Thr Ser Leu Gln Leu Val Thr
      930      935      940
Gln Met Thr Ser Glu Asp Leu Leu Arg Ile Gly Ile Thr Leu Ala Gly
945      950      955      960
His Gln Lys Lys Ile Leu Asn Ser Ile His Ser Met Xaa Val Gln Ile
      965      970      975
Ser Gln Ser Pro Thr Ala Met Ala
      980

```

<210> 295  
 <211> 1055  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 923  
 <223> Xaa = E or K

```

<400> 295
Met Ala Leu Arg Arg Leu Gly Ala Ala Leu Leu Leu Leu Pro Leu Leu
 1      5      10      15
Ala Ala Val Glu Glu Thr Leu Met Asp Ser Thr Thr Ala Thr Ala Glu
      20      25      30
Leu Gly Trp Met Val His Pro Pro Ser Gly Trp Glu Glu Val Ser Gly
      35      40      45
Tyr Asp Glu Asn Met Asn Thr Ile Arg Thr Tyr Gln Val Cys Asn Val
      50      55      60
Phe Glu Ser Ser Gln Asn Asn Trp Leu Arg Thr Lys Phe Ile Arg Arg
65      70      75      80
Arg Gly Ala His Arg Ile His Val Glu Met Lys Phe Ser Val Arg Asp
      85      90      95
Cys Ser Ser Ile Pro Ser Val Pro Gly Ser Cys Lys Glu Thr Phe Asn
      100      105      110
Leu Tyr Tyr Tyr Glu Ala Asp Phe Asp Ser Ala Thr Lys Thr Phe Pro
      115      120      125
Asn Trp Met Glu Asn Pro Trp Val Lys Val Asp Thr Ile Ala Ala Asp
      130      135      140
Glu Ser Phe Ser Gln Val Asp Leu Gly Gly Arg Val Met Lys Ile Asn
145      150      155      160
Thr Glu Val Arg Ser Phe Gly Pro Val Ser Arg Ser Gly Phe Tyr Leu

```

[illegible]

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610						615						620					
Gln	Val	Ile	Gly	Ala	Gly	Glu	Phe	Gly	Glu	Val	Cys	Ser	Gly	His	Leu		
625					630					635					640		
Lys	Leu	Pro	Gly	Lys	Arg	Glu	Ile	Phe	Val	Ala	Ile	Lys	Thr	Leu	Lys		
				645					650					655			
Ser	Gly	Tyr	Thr	Glu	Lys	Gln	Arg	Arg	Asp	Phe	Leu	Ser	Glu	Ala	Ser		
			660					665					670				
Ile	Met	Gly	Gln	Phe	Asp	His	Pro	Asn	Val	Ile	His	Leu	Glu	Gly	Val		
		675					680					685					
Val	Thr	Lys	Ser	Thr	Pro	Val	Met	Ile	Ile	Thr	Glu	Phe	Met	Glu	Asn		
	690					695					700						
Gly	Ser	Leu	Asp	Ser	Phe	Leu	Arg	Gln	Asn	Asp	Gly	Gln	Phe	Thr	Val		
705					710					715					720		
Ile	Gln	Leu	Val	Gly	Met	Leu	Arg	Gly	Ile	Ala	Ala	Gly	Met	Lys	Tyr		
				725				730						735			
Leu	Ala	Asp	Met	Asn	Tyr	Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile		
		740						745					750				
Leu	Val	Asn	Ser	Asn	Leu	Val	Cys	Lys	Val	Ser	Asp	Phe	Gly	Leu	Ser		
		755					760					765					
Arg	Phe	Leu	Glu	Asp	Asp	Thr	Ser	Asp	Pro	Thr	Tyr	Thr	Ser	Ala	Leu		
	770					775					780						
Gly	Gly	Lys	Ile	Pro	Ile	Arg	Trp	Thr	Ala	Pro	Glu	Ala	Ile	Gln	Tyr		
785					790					795					800		
Arg	Lys	Phe	Thr	Ser	Ala	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Ile	Val	Met		
				805					810					815			
Trp	Glu	Val	Met	Ser	Tyr	Gly	Glu	Arg	Pro	Tyr	Trp	Asp	Met	Thr	Asn		
		820						825					830				
Gln	Asp	Val	Ile	Asn	Ala	Ile	Glu	Gln	Asp	Tyr	Arg	Leu	Pro	Pro	Pro		
	835						840					845					
Met	Asp	Cys	Pro	Ser	Ala	Leu	His	Gln	Leu	Met	Leu	Asp	Cys	Trp	Gln		
	850						855				860						
Lys	Asp	Arg	Asn	His	Arg	Pro	Lys	Phe	Gly	Gln	Ile	Val	Asn	Thr	Leu		
865					870					875					880		
Asp	Lys	Met	Ile	Arg	Asn	Pro	Asn	Ser	Leu	Lys	Ala	Met	Ala	Pro	Leu		
				885					890					895			
Ser	Ser	Gly	Ile	Asn	Leu	Pro	Leu	Leu	Asp	Arg	Thr	Ile	Pro	Asp	Tyr		
		900						905					910				
Thr	Ser	Phe	Asn	Thr	Val	Asp	Glu	Trp	Leu	Xaa	Ala	Ile	Lys	Met	Gly		
		915					920						925				
Gln	Tyr	Lys	Glu	Ser	Phe	Ala	Asn	Ala	Gly	Phe	Thr	Ser	Phe	Asp	Val		
	930					935					940						
Val	Ser	Gln	Met	Met	Met	Glu	Asp	Ile	Leu	Arg	Val	Gly	Val	Thr	Leu		
945					950					955					960		
Ala	Gly	His	Gln	Lys	Lys	Ile	Leu	Asn	Ser	Ile	Gln	Val	Met	Arg	Ala		
				965					970					975			
Gln	Met	Asn	Gln	Ile	Gln	Ser	Val	Glu	Gly	Gln	Pro	Leu	Ala	Arg	Arg		
			980					985					990				
Pro	Arg	Ala	Thr	Gly	Arg	Thr	Lys	Arg	Cys	Gln	Pro	Arg	Asp	Val	Thr		
		995					1000						1005				
Lys	Lys	Thr	Cys	Asn	Ser	Asn	Asp	Gly	Lys	Lys	Lys	Gly	Met	Gly	Lys		
	1010					1015					1020						
Lys	Lys	Thr	Asp	Pro	Gly	Arg	Gly	Arg	Glu	Ile	Gln	Gly	Ile	Phe	Phe		
1025					1030					1035					1040		
Lys	Glu	Asp	Ser	His	Lys	Glu	Ser	Asn	Asp	Cys	Ser	Cys	Gly	Gly			
				1045					1050				1055				

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<210> 296  
 <211> 998  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 981  
 <223> Xaa = S or I

<400> 296  
 Met Ala Arg Ala Arg Pro Pro Pro Pro Pro Ser Pro Pro Pro Gly Leu  
 1 5 10 15  
 Leu Pro Leu Leu Pro Pro Leu Leu Leu Leu Pro Leu Leu Leu Leu Pro  
 20 25 30  
 Ala Gly Cys Arg Ala Leu Glu Glu Thr Leu Met Asp Thr Lys Trp Val  
 35 40 45  
 Thr Ser Glu Leu Ala Trp Thr Ser His Pro Glu Ser Gly Trp Glu Glu  
 50 55 60  
 Val Ser Gly Tyr Asp Glu Ala Met Asn Pro Ile Arg Thr Tyr Gln Val  
 65 70 75 80  
 Cys Asn Val Arg Glu Ser Ser Gln Asn Asn Trp Leu Arg Thr Gly Phe  
 85 90 95  
 Ile Trp Arg Arg Asp Val Gln Arg Val Tyr Val Glu Leu Lys Phe Thr  
 100 105 110  
 Val Arg Asp Cys Asn Ser Ile Pro Asn Ile Pro Gly Ser Cys Lys Glu  
 115 120 125  
 Thr Phe Asn Leu Phe Tyr Tyr Glu Ala Asp Ser Asp Val Ala Ser Ala  
 130 135 140  
 Ser Ser Pro Phe Trp Met Glu Asn Pro Tyr Val Lys Val Asp Thr Ile  
 145 150 155 160  
 Ala Pro Asp Glu Ser Phe Ser Arg Leu Asp Ala Gly Arg Val Asn Thr  
 165 170 175  
 Lys Val Arg Ser Phe Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu Ala  
 180 185 190  
 Phe Gln Asp Gln Gly Ala Cys Met Ser Leu Ile Ser Val Arg Ala Phe  
 195 200 205  
 Tyr Lys Lys Cys Ala Ser Thr Thr Ala Gly Phe Ala Leu Phe Pro Glu  
 210 215 220  
 Thr Leu Thr Gly Ala Glu Pro Thr Ser Leu Val Ile Ala Pro Gly Thr  
 225 230 235 240  
 Cys Ile Pro Asn Ala Val Glu Val Ser Val Pro Leu Lys Leu Tyr Cys  
 245 250 255  
 Asn Gly Asp Gly Glu Trp Met Val Pro Val Gly Ala Cys Thr Cys Ala  
 260 265 270  
 Thr Gly His Glu Pro Ala Ala Lys Glu Ser Gln Cys Arg Pro Cys Pro  
 275 280 285  
 Pro Gly Ser Tyr Lys Ala Lys Gln Gly Glu Gly Pro Cys Leu Pro Cys  
 290 295 300  
 Pro Pro Asn Ser Arg Thr Thr Ser Pro Ala Ala Ser Ile Cys Thr Cys  
 305 310 315 320  
 His Asn Asn Phe Tyr Arg Ala Asp Ser Asp Ser Ala Asp Ser Ala Cys  
 325 330 335  
 Thr Thr Val Pro Ser Pro Pro Arg Gly Val Ile Ser Asn Val Asn Glu  
 340 345 350



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Thr Ser Leu Ile Leu Glu Trp Ser Glu Pro Arg Asp Leu Gly Gly Arg  
 355 360 365  
 Asp Asp Leu Leu Tyr Asn Val Ile Cys Lys Lys Cys His Gly Ala Gly  
 370 375 380  
 Gly Ala Ser Ala Cys Ser Arg Cys Asp Asp Asn Val Glu Phe Val Pro  
 385 390 395 400  
 Arg Gln Leu Gly Leu Thr Glu Arg Arg Val His Ile Ser His Leu Leu  
 405 410 415  
 Ala His Thr Arg Tyr Thr Phe Glu Val Gln Ala Val Asn Gly Val Ser  
 420 425 430  
 Gly Lys Ser Pro Leu Pro Pro Arg Tyr Ala Ala Val Asn Ile Thr Thr  
 435 440 445  
 Asn Gln Ala Ala Pro Ser Glu Val Pro Thr Leu Arg Leu His Ser Ser  
 450 455 460  
 Ser Gly Ser Ser Leu Thr Leu Ser Trp Ala Pro Pro Glu Arg Pro Asn  
 465 470 475 480  
 Gly Val Ile Leu Asp Tyr Glu Met Lys Tyr Phe Glu Lys Ser Glu Gly  
 485 490 495  
 Ile Ala Ser Thr Val Thr Ser Gln Met Asn Ser Val Gln Leu Asp Gly  
 500 505 510  
 Leu Arg Pro Asp Ala Arg Tyr Val Val Gln Val Arg Ala Arg Thr Val  
 515 520 525  
 Ala Gly Tyr Gly Gln Tyr Ser Arg Pro Ala Glu Phe Glu Thr Thr Ser  
 530 535 540  
 Glu Arg Gly Ser Gly Ala Gln Gln Leu Gln Glu Gln Leu Pro Leu Ile  
 545 550 555 560  
 Val Gly Ser Ala Thr Ala Gly Leu Val Phe Val Val Ala Val Val Val  
 565 570 575  
 Ile Ala Ile Val Cys Leu Arg Lys Gln Arg His Gly Ser Asp Ser Glu  
 580 585 590  
 Tyr Thr Glu Lys Leu Gln Gln Tyr Ile Ala Pro Gly Met Lys Val Tyr  
 595 600 605  
 Ile Asp Pro Phe Thr Tyr Glu Asp Pro Asn Glu Ala Val Arg Glu Phe  
 610 615 620  
 Ala Lys Glu Ile Asp Val Ser Cys Val Lys Ile Glu Glu Val Ile Gly  
 625 630 635 640  
 Ala Gly Glu Phe Gly Glu Val Cys Arg Gly Arg Leu Lys Gln Pro Gly  
 645 650 655  
 Arg Arg Glu Val Phe Val Ala Ile Lys Thr Leu Lys Val Gly Tyr Thr  
 660 665 670  
 Glu Arg Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser Ile Met Gly Gln  
 675 680 685  
 Phe Asp His Pro Asn Ile Ile Arg Leu Glu Gly Val Val Thr Lys Ser  
 690 695 700  
 Arg Pro Val Met Ile Leu Thr Glu Phe Met Glu Asn Cys Ala Leu Asp  
 705 710 715 720  
 Ser Phe Leu Arg Leu Asn Asp Gly Gln Phe Thr Val Ile Gln Leu Val  
 725 730 735  
 Gly Met Leu Arg Gly Ile Ala Ala Gly Met Lys Tyr Leu Ser Glu Met  
 740 745 750  
 Asn Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser  
 755 760 765  
 Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Phe Leu Glu  
 770 775 780  
 Asp Asp Pro Ser Asp Pro Thr Tyr Thr Ser Ser Leu Gly Gly Lys Ile  
 785 790 795 800

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Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Ala Tyr Arg Lys Phe Thr
      805      810      815
Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met Trp Glu Val Met
      820      825      830
Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp Val Ile
      835      840      845
Asn Ala Val Glu Gln Asp Tyr Arg Leu Pro Pro Pro Met Asp Cys Pro
      850      855      860
Thr Ala Leu His Gln Leu Met Leu Asp Cys Trp Val Arg Asp Arg Asn
      865      870      875      880
Leu Arg Pro Lys Phe Ser Gln Ile Val Asn Thr Leu Asp Lys Leu Ile
      885      890      895
Arg Asn Ala Ala Ser Leu Lys Val Ile Ala Ser Ala Gln Ser Gly Met
      900      905      910
Ser Gln Pro Leu Leu Asp Arg Thr Val Pro Asp Tyr Thr Thr Phe Thr
      915      920      925
Thr Val Gly Asp Trp Leu Asp Ala Ile Lys Met Gly Arg Tyr Lys Glu
      930      935      940
Ser Phe Val Ser Ala Gly Phe Ala Ser Phe Asp Leu Val Ala Gln Met
      945      950      955      960
Thr Ala Glu Asp Leu Leu Arg Ile Gly Val Thr Leu Ala Gly His Gln
      965      970      975
Lys Lys Ile Leu Xaa Ser Ile Gln Asp Met Arg Leu Gln Met Asn Gln
      980      985      990
Thr Leu Pro Val Gln Val
      995

```

```

<210> 297
<211> 987
<212> PRT
<213> Homo sapiens

```

```

<220>
<221> VARIANT
<222> 463
<223> Xaa = A or D

```

```

<220>
<221> VARIANT
<222> 471
<223> Xaa = Y or D

```

```

<220>
<221> VARIANT
<222> 926
<223> Xaa = E or D

```

```

<400> 297
Met Glu Leu Arg Val Leu Leu Cys Trp Ala Ser Leu Ala Ala Ala Leu
  1      5      10      15
Glu Glu Thr Leu Leu Asn Thr Lys Leu Glu Thr Ala Asp Leu Lys Trp
      20      25      30
Val Thr Phe Pro Gln Val Asp Gly Gln Trp Glu Glu Leu Ser Gly Leu
      35      40      45
Asp Glu Glu Gln His Ser Val Arg Thr Tyr Glu Val Cys Asp Val Gln

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50	55	60
Arg Ala Pro Gly Gln Ala His Trp Leu Arg Thr Gly Trp Val Pro Arg		
65	70	75
Arg Gly Ala Val His Val Tyr Ala Thr Leu Arg Phe Thr Met Leu Glu		
	85	90
Cys Leu Ser Leu Pro Arg Ala Gly Arg Ser Cys Lys Glu Thr Phe Thr		
	100	105
Val Phe Tyr Tyr Glu Ser Asp Ala Asp Thr Ala Thr Ala Leu Thr Pro		
	115	120
Ala Trp Met Glu Asn Pro Tyr Ile Lys Val Asp Thr Val Ala Ala Glu		
	130	135
His Leu Thr Arg Lys Arg Pro Gly Ala Glu Ala Thr Gly Lys Val Asn		
	145	150
Val Lys Thr Leu Arg Leu Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu		
	165	170
Ala Phe Gln Asp Gln Gly Ala Cys Met Ala Leu Leu Ser Leu His Leu		
	180	185
Phe Tyr Lys Lys Cys Ala Gln Leu Thr Val Asn Leu Thr Arg Phe Pro		
	195	200
Glu Thr Val Pro Arg Glu Leu Val Val Pro Val Ala Gly Ser Cys Val		
	210	215
Val Asp Ala Val Pro Ala Pro Gly Pro Ser Pro Ser Leu Tyr Cys Arg		
	225	230
Glu Asp Gly Gln Trp Ala Glu Gln Pro Val Thr Gly Cys Ser Cys Ala		
	245	250
Pro Gly Phe Glu Ala Ala Glu Gly Asn Thr Lys Cys Arg Ala Cys Ala		
	260	265
Gln Gly Thr Phe Lys Pro Leu Ser Gly Glu Gly Ser Cys Gln Pro Cys		
	275	280
Pro Ala Asn Ser His Ser Asn Thr Ile Gly Ser Ala Val Cys Gln Cys		
	290	295
Arg Val Gly Tyr Phe Arg Ala Arg Thr Asp Pro Arg Gly Ala Pro Cys		
	305	310
Thr Thr Pro Pro Ser Ala Pro Arg Ser Val Val Ser Arg Leu Asn Gly		
	325	330
Ser Ser Leu His Leu Glu Trp Ser Ala Pro Leu Glu Ser Gly Gly Arg		
	340	345
Glu Asp Leu Thr Tyr Ala Leu Arg Cys Arg Glu Cys Arg Pro Gly Gly		
	355	360
Ser Cys Ala Pro Cys Gly Gly Asp Leu Thr Phe Asp Pro Gly Pro Arg		
	370	375
Asp Leu Val Glu Pro Trp Val Val Val Arg Gly Leu Arg Pro Asp Phe		
	385	390
Thr Tyr Thr Phe Glu Val Thr Ala Leu Asn Gly Val Ser Ser Leu Ala		
	405	410
Thr Gly Pro Val Pro Phe Glu Pro Val Asn Val Thr Thr Asp Arg Glu		
	420	425
Val Pro Pro Ala Val Ser Asp Ile Arg Val Thr Arg Ser Ser Pro Ser		
	435	440
Ser Leu Ser Leu Ala Trp Ala Val Pro Arg Ala Pro Ser Gly Xaa Val		
	450	455
Leu Asp Tyr Glu Val Lys Xaa His Glu Lys Gly Ala Glu Gly Pro Ser		
	465	470
Ser Val Arg Phe Leu Lys Thr Ser Glu Asn Arg Ala Glu Leu Arg Gly		
	485	490
Leu Lys Arg Gly Ala Ser Tyr Leu Val Gln Val Arg Ala Arg Ser Glu		

			500					505					510			
Ala	Gly	Tyr	Gly	Pro	Phe	Gly	Gln	Glu	His	His	Ser	Gln	Thr	Gln	Leu	
		515					520					525				
Asp	Glu	Ser	Glu	Gly	Trp	Arg	Glu	Gln	Leu	Ala	Leu	Ile	Ala	Gly	Thr	
		530					535					540				
Ala	Val	Val	Gly	Val	Val	Leu	Val	Leu	Val	Val	Ile	Val	Val	Ala	Val	
545					550					555					560	
Leu	Cys	Leu	Arg	Lys	Gln	Ser	Asn	Gly	Arg	Glu	Ala	Glu	Tyr	Ser	Asp	
				565					570					575		
Lys	His	Gly	Gln	Tyr	Leu	Ile	Gly	His	Gly	Thr	Lys	Val	Tyr	Ile	Asp	
			580					585					590			
Pro	Phe	Thr	Tyr	Glu	Asp	Pro	Asn	Glu	Ala	Val	Arg	Glu	Phe	Ala	Lys	
		595					600					605				
Glu	Ile	Asp	Val	Ser	Tyr	Val	Lys	Ile	Glu	Glu	Val	Ile	Gly	Ala	Gly	
		610					615					620				
Glu	Phe	Gly	Glu	Val	Cys	Arg	Gly	Arg	Leu	Lys	Ala	Pro	Gly	Lys	Lys	
625					630					635					640	
Glu	Ser	Cys	Val	Ala	Ile	Lys	Thr	Leu	Lys	Gly	Gly	Tyr	Thr	Glu	Arg	
				645					650					655		
Gln	Arg	Arg	Glu	Phe	Leu	Ser	Glu	Ala	Ser	Ile	Met	Gly	Gln	Phe	Glu	
			660					665					670			
His	Pro	Asn	Ile	Ile	Arg	Leu	Glu	Gly	Val	Val	Thr	Asn	Ser	Met	Pro	
		675					680					685				
Val	Met	Ile	Leu	Thr	Glu	Phe	Met	Glu	Asn	Gly	Ala	Leu	Asp	Ser	Phe	
		690					695				700					
Leu	Arg	Leu	Asn	Asp	Gly	Gln	Phe	Thr	Val	Ile	Gln	Leu	Val	Gly	Met	
705					710					715					720	
Leu	Arg	Gly	Ile	Ala	Ser	Gly	Met	Arg	Tyr	Leu	Ala	Glu	Met	Ser	Tyr	
				725					730					735		
Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Val	Asn	Ser	Asn	Leu	
			740					745					750			
Val	Cys	Lys	Val	Ser	Asp	Phe	Gly	Leu	Ser	Arg	Phe	Leu	Glu	Glu	Asn	
		755					760					765				
Ser	Ser	Asp	Pro	Thr	Tyr	Thr	Ser	Ser	Leu	Gly	Gly	Lys	Ile	Pro	Ile	
		770					775					780				
Arg	Trp	Thr	Ala	Pro	Glu	Ala	Ile	Ala	Phe	Arg	Lys	Phe	Thr	Ser	Ala	
785					790				795						800	
Ser	Asp	Ala	Trp	Ser	Tyr	Gly	Ile	Val	Met	Trp	Glu	Val	Met	Ser	Phe	
				805					810					815		
Gly	Glu	Arg	Pro	Tyr	Trp	Asp	Met	Ser	Asn	Gln	Asp	Val	Ile	Asn	Ala	
			820					825					830			
Ile	Glu	Gln	Asp	Tyr	Arg	Leu	Pro	Pro	Pro	Pro	Asp	Cys	Pro	Thr	Ser	
		835					840					845				
Leu	His	Gln	Leu	Met	Leu	Asp	Cys	Trp	Gln	Lys	Asp	Arg	Asn	Ala	Arg	
		850				855				</						

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945                                      950                                      955                                      960  
 Ile Leu Ala Ser Val Gln His Met Lys Ser Gln Ala Lys Pro Gly Thr  
    965                                      970                                      975  
 Pro Gly Gly Thr Gly Gly Pro Ala Pro Gln Tyr  
    980                                      985

<210> 298  
 <211> 1006  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 107  
 <223> Xaa = G or S

<220>  
 <221> VARIANT  
 <222> 267  
 <223> Xaa = P or R

<220>  
 <221> VARIANT  
 <222> 309  
 <223> Xaa = S or A

<220>  
 <221> VARIANT  
 <222> 484  
 <223> Xaa = R or Q

<400> 298  
 Met Val Cys Ser Leu Trp Val Leu Leu Leu Val Ser Ser Val Leu Ala  
 1                                      5                                      10                                      15  
 Leu Glu Glu Val Leu Leu Asp Thr Thr Gly Glu Thr Ser Glu Ile Gly  
    20                                      25                                      30  
 Trp Leu Thr Tyr Pro Pro Gly Gly Trp Asp Glu Val Ser Val Leu Asp  
    35                                      40                                      45  
 Asp Gln Arg Arg Leu Thr Arg Thr Phe Glu Ala Cys His Val Ala Gly  
 50                                      55                                      60  
 Ala Pro Pro Gly Thr Gly Gln Asp Asn Trp Leu Gln Thr His Phe Val  
 65                                      70                                      75                                      80  
 Glu Arg Arg Gly Ala Gln Arg Ala His Ile Arg Leu His Phe Ser Val  
    85                                      90                                      95  
 Arg Ala Cys Ser Ser Leu Gly Val Ser Gly Xaa Thr Cys Arg Glu Thr  
    100                                      105                                      110  
 Phe Thr Leu Tyr Tyr Arg Gln Ala Glu Glu Pro Asp Ser Pro Asp Ser  
    115                                      120                                      125  
 Val Ser Ser Trp His Leu Lys Arg Trp Thr Lys Val Asp Thr Ile Ala  
 130                                      135                                      140  
 Ala Asp Glu Ser Phe Pro Ser Ser Ser Ser Ser Ser Ser Ser Ser  
 145                                      150                                      155                                      160  
 Ser Ala Ala Trp Ala Val Gly Pro His Gly Ala Gly Gln Arg Ala Gly  
    165                                      170                                      175  
 Leu Gln Leu Asn Val Lys Glu Arg Ser Phe Gly Pro Leu Thr Gln Arg

				180						185				190		
Gly	Phe	Tyr	Val	Ala	Phe	Gln	Asp	Thr	Gly	Ala	Cys	Leu	Ala	Leu	Val	
		195					200					205				
Ala	Val	Arg	Leu	Phe	Ser	Tyr	Thr	Cys	Pro	Ala	Val	Leu	Arg	Ser	Phe	
		210					215					220				
Ala	Ser	Phe	Pro	Glu	Thr	Gln	Ala	Ser	Gly	Ala	Gly	Gly	Ala	Ser	Leu	
225					230					235					240	
Val	Ala	Ala	Val	Gly	Thr	Cys	Val	Ala	His	Ala	Glu	Pro	Glu	Glu	Asp	
				245						250					255	
Gly	Val	Gly	Gly	Gln	Ala	Gly	Gly	Ser	Pro	Xaa	Arg	Leu	His	Cys	Asn	
			260						265					270		
Gly	Glu	Gly	Lys	Trp	Met	Val	Ala	Val	Gly	Gly	Cys	Arg	Cys	Gln	Pro	
		275					280						285			
Gly	Tyr	Gln	Pro	Ala	Arg	Gly	Asp	Lys	Ala	Cys	Gln	Ala	Cys	Pro	Arg	
		290					295				300					
Gly	Leu	Tyr	Lys	Xaa	Ser	Ala	Gly	Asn	Ala	Pro	Cys	Ser	Pro	Cys	Pro	
305					310					315					320	
Ala	Arg	Ser	His	Ala	Pro	Asn	Pro	Ala	Ala	Pro	Val	Cys	Pro	Cys	Leu	
				325						330					335	
Glu	Gly	Phe	Tyr	Arg	Ala	Ser	Ser	Asp	Pro	Pro	Glu	Ala	Pro	Cys	Thr	
			340					345					350			
Gly	Pro	Pro	Ser	Ala	Pro	Gln	Glu	Leu	Trp	Phe	Glu	Val	Gln	Gly	Ser	
		355					360					365				
Ala	Leu	Met	Leu	His	Trp	Arg	Leu	Pro	Arg	Glu	Leu	Gly	Gly	Arg	Gly	
		370				375					380					
Asp	Leu	Leu	Phe	Asn	Val	Val	Cys	Lys	Glu	Cys	Glu	Gly	Arg	Gln	Glu	
385				390						395					400	
Pro	Ala	Ser	Gly	Gly	Gly	Thr	Cys	His	Arg	Cys	Arg	Asp	Glu	Val		
			405						410				415			
His	Phe	Asp	Pro	Arg	Gln	Arg	Gly	Leu	Thr	Glu	Ser	Arg	Val	Leu	Val	
			420						425				430			
Gly	Gly	Leu	Arg	Ala	His	Val	Pro	Tyr	Ile	Leu	Glu	Val	Gln	Ala	Val	
		435					440					445				
Asn	Gly	Val	Ser	Glu	Leu	Ser	Pro	Asp	Pro	Pro	Gln	Ala	Ala	Ala	Ile	
		450				455					460					
Asn	Val	Ser	Thr	Ser	His	Glu	Val	Ser	Ala	Val	Pro	Val	Val	Val	His	
465					470					475					480	
Gln	Val	Ser	Xaa	Ala	Ser	Asn	Ser	Ile	Thr	Val	Ser	Trp	Pro	Gln	Pro	
			485						490				495			
Asp	Gln	Thr	Asn	Gly	Asn	Ile	Leu	Asp	Tyr	Gln	Leu	Arg	Tyr	Tyr	Asp	
			500					505					510			
Gln	Ala	Glu	Asp	Glu	Ser	His	Ser	Phe	Thr	Leu	Thr	Ser	Glu	Thr	Asn	
		515					520									

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625					630					635				640	
Gln	Ala	Ile	Arg	Glu	Leu	Ala	Arg	Glu	Val	Asp	Pro	Ala	Tyr	Ile	Lys
				645					650					655	
Ile	Glu	Glu	Val	Ile	Gly	Thr	Gly	Ser	Phe	Gly	Glu	Val	Arg	Gln	Gly
			660					665					670		
Arg	Leu	Gln	Pro	Arg	Gly	Arg	Arg	Glu	Gln	Thr	Val	Ala	Ile	Gln	Ala
		675					680					685			
Leu	Trp	Ala	Gly	Gly	Ala	Glu	Ser	Leu	Gln	Met	Thr	Phe	Leu	Gly	Arg
	690					695					700				
Ala	Ala	Val	Leu	Gly	Gln	Phe	Gln	His	Pro	Asn	Ile	Leu	Arg	Leu	Glu
705					710					715					720
Gly	Val	Val	Thr	Lys	Ser	Arg	Pro	Leu	Met	Val	Leu	Thr	Glu	Phe	Met
				725					730					735	
Glu	Leu	Gly	Pro	Leu	Asp	Ser	Phe	Leu	Arg	Gln	Arg	Glu	Gly	Gln	Phe
			740					745					750		
Ser	Ser	Leu	Gln	Leu	Val	Ala	Met	Gln	Arg	Gly	Val	Ala	Ala	Ala	Met
		755					760					765			
Gln	Tyr	Leu	Ser	Ser	Phe	Ala	Phe	Val	His	Arg	Ser	Leu	Ser	Ala	His
	770					775					780				
Ser	Val	Leu	Val	Asn	Ser	His	Leu	Val	Cys	Lys	Val	Ala	Arg	Leu	Gly
785					790					795					800
His	Ser	Pro	Gln	Gly	Pro	Ser	Cys	Leu	Leu	Arg	Trp	Ala	Ala	Pro	Glu
				805					810					815	
Val	Ile	Ala	His	Gly	Lys	His	Thr	Thr	Ser	Ser	Asp	Val	Trp	Ser	Phe
			820					825					830		
Gly	Ile	Leu	Met	Trp	Glu	Val	Met	Ser	Tyr	Gly	Glu	Arg	Pro	Tyr	Trp
		835					840					845			
Asp	Met	Ser	Glu	Gln	Glu	Val	Leu	Asn	Ala	Ile	Glu	Gln	Glu	Phe	Arg
	850					855					860				
Leu	Pro	Pro	Pro	Pro	Gly	Cys	Pro	Pro	Gly	Leu	His	Leu	Leu	Met	Leu
865					870					875					880
Asp	Thr	Trp	Gln	Lys	Asp	Arg	Ala	Arg	Arg	Pro	His	Phe	Asp	Gln	Leu
				885					890					895	
Val	Ala	Ala	Phe	Asp	Lys	Met	Ile	Arg	Lys	Pro	Asp	Thr	Leu	Gln	Ala
			900					905					910		
Gly	Gly	Asp	Pro	Gly	Glu	Arg	Pro	Ser	Gln	Ala	Leu	Leu	Thr	Pro	Val
		915					920					925			
Ala	Leu	Asp	Phe	Pro	Cys	Leu	Asp	Ser	Pro	Gln	Ala	Trp	Leu	Ser	Ala
	930						935				940				
Ile	Gly	Leu	Glu	Cys	Tyr	Gln	Asp	Asn	Phe	Ser	Lys	Phe	Gly	Leu	Cys
945					950					955					960
Thr	Phe	Ser	Asp	Val	Ala	Gln	Leu	Ser	Leu	Glu	Asp	Leu	Pro	Ala	Leu
			965						970					975	
Gly	Ile	Thr	Leu	Ala	Gly	His	Gln	Lys	Lys	Leu	Leu	His	His	Ile	Gln
			980				985						990		
Leu	Leu	Gln	Gln	His	Leu	Arg	Gln	Gln	Gly	Ser	Val	Glu	Val		
		995					1000					1005			

&lt;210&gt; 299

&lt;211&gt; 1255

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

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&lt;222&gt; 655

&lt;223&gt; Xaa = I or V

&lt;400&gt; 299

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Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1          5          10          15
Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
      20          25          30
Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
      35          40          45
Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
      50          55          60
Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
      65          70          75          80
Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
      85          90          95
Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
      100          105          110
Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
      115          120          125
Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
      130          135          140
Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
      145          150          155          160
Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
      165          170          175
Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
      180          185          190
His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
      195          200          205
Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
      210          215          220
Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
      225          230          235
Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
      245          250          255
His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
      260          265          270
Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
      275          280          285
Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
      290          295          300
Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
      305          310          315          320
Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
      325          330          335
Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu
      340          345          350
Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys
      355          360          365
Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp
      370          375          380
Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe
      385          390          395          400
Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro
      405          410          415

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Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg  
                   420                  425                  430  
 Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu  
                   435                  440                  445  
 Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly  
                   450                  455                  460  
 Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His Thr Val  
                   465                  470                  475                  480  
 Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr  
                   485                  490                  495  
 Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala Cys His  
                   500                  505                  510  
 Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys  
                   515                  520                  525  
 Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu Cys  
                   530                  535                  540  
 Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg His Cys  
                   545                  550                  555                  560  
 Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys  
                   565                  570                  575  
 Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp  
                   580                  585                  590  
 Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu  
                   595                  600                  605  
 Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln  
                   610                  615                  620  
 Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys  
                   625                  630                  635                  640  
 Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile Xaa Ser  
                   645                  650                  655  
 Ala Val Val Gly Ile Leu Leu Val Val Val Leu Gly Val Val Phe Gly  
                   660                  665                  670  
 Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr Met Arg  
                   675                  680                  685  
 Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly  
                   690                  695                  700  
 Ala Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu Leu  
                   705                  710                  715                  720  
 Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys  
                   725                  730                  735  
 Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val Ala Ile  
                   740                  745                  750  
 Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu  
                   755                  760                  765  
 Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser Arg  
                   770                  775                  780  
 Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln Leu  
                   785                  790                  795                  800  
 Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu Asn Arg Gly Arg  
                   805                  810                  815  
 Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Met Gln Ile Ala Lys Gly  
                   820                  825                  830  
 Met Ser Tyr Leu Glu Asp Val Arg Leu Val His Arg Asp Leu Ala Ala  
                   835                  840                  845  
 Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe  
                   850                  855                  860

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Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala Asp  
 865 870 875 880  
 Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu Arg  
 885 890 895  
 Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val  
 900 905 910  
 Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala  
 915 920 925  
 Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro  
 930 935 940  
 Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met  
 945 950 955 960  
 Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu Phe  
 965 970 975  
 Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu  
 980 985 990  
 Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu  
 995 1000 1005  
 Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr Leu  
 1010 1015 1020  
 Val Pro Gln Gln Gly Phe Cys Pro Asp Pro Ala Pro Gly Ala Gly  
 1025 1030 1035 1040  
 Gly Met Val His His Arg His Arg Ser Ser Ser Thr Arg Ser Gly Gly  
 1045 1050 1055  
 Gly Asp Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu Glu Ala Pro Arg  
 1060 1065 1070  
 Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser Asp Val Phe Asp Gly  
 1075 1080 1085  
 Asp Leu Gly Met Gly Ala Ala Lys Gly Leu Gln Ser Leu Pro Thr His  
 1090 1095 1100  
 Asp Pro Ser Pro Leu Gln Arg Tyr Ser Glu Asp Pro Thr Val Pro Leu  
 1105 1110 1115 1120  
 Pro Ser Glu Thr Asp Gly Tyr Val Ala Pro Leu Thr Cys Ser Pro Gln  
 1125 1130 1135  
 Pro Glu Tyr Val Asn Gln Pro Asp Val Arg Pro Gln Pro Pro Ser Pro  
 1140 1145 1150  
 Arg Glu Gly Pro Leu Pro Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu  
 1155 1160 1165  
 Arg Pro Lys Thr Leu Ser Pro Gly Lys Asn Gly Val Val Lys Asp Val  
 1170 1175 1180  
 Phe Ala Phe Gly Gly Ala Val Glu Asn Pro Glu Tyr Leu Thr Pro Gln  
 1185 1190 1195 1200  
 Gly Gly Ala Ala Pro Gln Pro His Pro Pro Ala Phe Ser Pro Ala  
 1205 1210 1215  
 Phe Asp Asn Leu Tyr Tyr Trp Asp Gln Asp Pro Pro Glu Arg Gly Ala  
 1220 1225 1230  
 Pro Pro Ser Thr Phe Lys Gly Thr Pro Thr Ala Glu Asn Pro Glu Tyr  
 1235 1240 1245  
 Leu Gly Leu Asp Val Pro Val  
 1250 1255

&lt;210&gt; 300

&lt;211&gt; 820

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

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<223> Xaa = G or D

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<223> Xaa = Y or C

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<223> Xaa = P or R

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<223> Xaa = V or M

<220>  
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<223> Xaa = W or R

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 <223> Xaa = G or R

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 20 25 30  
 Pro Trp Gly Ala Pro Val Glu Val Glu Ser Phe Leu Val His Pro Gly  
 35 40 45  
 Asp Leu Leu Gln Leu Arg Cys Arg Leu Arg Asp Asp Val Gln Ser Ile  
 50 55 60  
 Asn Trp Leu Arg Asp Gly Val Gln Leu Ala Glu Ser Asn Arg Thr Arg  
 65 70 75 80  
 Ile Thr Gly Glu Glu Val Glu Val Gln Asp Ser Val Pro Ala Asp Ser  
 85 90 95  
 Xaa Leu Xaa Ala Cys Val Thr Ser Ser Pro Ser Gly Ser Asp Thr Thr  
 100 105 110  
 Tyr Phe Ser Val Asn Val Ser Asp Ala Leu Pro Ser Ser Glu Asp Asp  
 115 120 125  
 Asp Asp Asp Asp Asp Ser Ser Ser Glu Glu Lys Glu Thr Asp Asn Thr  
 130 135 140  
 Lys Pro Asn Pro Val Ala Pro Tyr Trp Thr Ser Pro Glu Lys Met Glu  
 145 150 155 160  
 Lys Lys Leu His Xaa Val Pro Ala Ala Lys Thr Val Lys Phe Lys Cys  
 165 170 175  
 Pro Ser Ser Gly Thr Pro Asn Pro Thr Leu Arg Trp Leu Xaa Asn Xaa  
 180 185 190  
 Lys Glu Phe Lys Pro Xaa His Arg Ile Gly Gly Tyr Lys Val Arg Tyr  
 195 200 205  
 Ala Thr Trp Ser Ile Ile Met Asp Ser Val Val Pro Ser Asp Lys Gly  
 210 215 220  
 Asn Tyr Thr Cys Ile Val Glu Asn Glu Tyr Gly Ser Ile Asn His Thr  
 225 230 235 240  
 Tyr Gln Leu Asp Val Val Glu Arg Ser Xaa His Arg Pro Ile Leu Gln  
 245 250 255  
 Ala Gly Leu Pro Ala Asn Lys Thr Val Ala Leu Gly Ser Asn Val Glu  
 260 265 270  
 Phe Met Xaa Lys Val Tyr Ser Asp Pro Gln Pro His Ile Gln Trp Leu  
 275 280 285  
 Lys His Ile Glu Val Asn Gly Ser Lys Ile Gly Pro Asp Asn Leu Pro  
 290 295 300  
 Tyr Val Gln Ile Leu Lys Thr Ala Gly Val Asn Thr Thr Asp Lys Glu  
 305 310 315 320  
 Met Glu Val Leu His Leu Arg Asn Val Ser Phe Glu Asp Ala Gly Glu  
 325 330 335  
 Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Leu Ser His His Ser Ala  
 340 345 350  
 Trp Leu Thr Val Leu Glu Ala Leu Glu Glu Arg Pro Ala Val Met Thr

Ser	Pro	Leu	Tyr	Leu	Glu	Ile	Ile	Ile	Tyr	Cys	Thr	Gly	Ala	Phe	Leu
	370					375					380				
Ile	Ser	Cys	Met	Val	Gly	Ser	Val	Ile	Val	Tyr	Lys	Met	Lys	Ser	Gly
385					390					395					400
Thr	Lys	Lys	Ser	Asp	Phe	His	Ser	Gln	Met	Ala	Val	His	Lys	Leu	Ala
				405					410					415	
Lys	Ser	Ile	Pro	Leu	Arg	Arg	Gln	Val	Thr	Val	Ser	Ala	Asp	Ser	Ser
			420					425					430		
Ala	Ser	Met	Asn	Ser	Gly	Val	Leu	Leu	Val	Arg	Pro	Ser	Arg	Leu	Ser
		435				440						445			
Ser	Ser	Gly	Thr	Pro	Met	Leu	Ala	Gly	Val	Ser	Glu	Tyr	Glu	Leu	Pro
	450					455					460				
Glu	Asp	Pro	Arg	Trp	Glu	Leu	Pro	Arg	Asp	Arg	Leu	Val	Leu	Gly	Lys
465					470					475					480
Pro	Leu	Gly	Glu	Gly	Cys	Phe	Gly	Gln	Val	Val	Leu	Ala	Glu	Ala	Ile
				485					490					495	
Gly	Leu	Asp	Lys	Asp	Lys	Pro	Asn	Arg	Val	Thr	Lys	Val	Ala	Val	Lys
			500					505					510		
Met	Leu	Lys	Ser	Asp	Ala	Thr	Glu	Lys	Asp	Leu	Ser	Asp	Leu	Ile	Ser
		515					520					525			
Glu	Met	Glu	Met	Met	Lys	Met	Ile	Gly	Lys	His	Lys	Asn	Ile	Ile	Asn
	530					535					540				
Leu	Leu	Gly	Ala	Cys	Thr	Gln	Asp	Gly	Pro	Leu	Tyr	Val	Ile	Val	Glu
545					550					555					560
Tyr	Ala	Ser	Lys	Gly	Asn	Leu	Arg	Glu	Tyr	Leu	Gln	Ala	Arg	Arg	Pro
				565				570						575	
Pro	Gly	Leu	Glu	Tyr	Cys	Tyr	Asn	Pro	Ser	His	Asn	Pro	Glu	Glu	Gln
			580					585					590		
Leu	Ser	Ser	Lys	Asp	Leu	Val	Ser	Cys	Ala	Tyr	Gln	Xaa	Ala	Arg	Gly
		595					600					605			
Met	Glu	Tyr	Leu	Ala	Ser	Lys	Lys	Cys	Ile	His	Arg	Asp	Leu	Ala	Ala
	610					615					620				
Arg	Asn	Val	Leu	Val	Thr	Glu	Asp	Asn	Val	Met	Lys	Ile	Ala	Asp	Phe
625					630					635					640
Gly	Leu	Ala	Arg	Asp	Ile	His	His	Ile	Asp	Tyr	Tyr	Lys	Lys	Thr	Thr
				645					650					655	
Asn	Gly	Arg	Leu	Pro	Val	Lys	Xaa	Met	Ala	Pro	Glu	Ala	Leu	Phe	Asp
			660					665					670		
Arg	Ile	Tyr	Thr	His	Gln	Ser	Asp	Val	Trp	Ser	Phe	Gly	Val	Leu	Leu
		675					680					685			
Trp	Glu	Ile	Phe	Thr	Leu	Gly	Gly	Ser	Pro	Tyr	Pro	Gly	Val	Pro	Val
	690					695					700				
Glu	Glu	Leu	Phe	Lys	Leu	Leu	Lys	Glu	Gly	His	Arg	Xaa	Asp	Lys	Pro
705					710										

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	805	810	815
Leu Lys Arg Xaa			
820			
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<211>	821		
<212>	PRT		
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<222>	162, 186		
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<223> Xaa = C or F

<220>  
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<223> Xaa = Y or C

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<223> Xaa = Q or P

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<223> Xaa = A or S

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<223> Xaa = Y or H

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<223> Xaa = T or P

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<223> Xaa = C or R or Y or S or F or W

<220>  
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<222> 344  
<223> Xaa = A or P or G

<220>  
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<222> 347, 351, 372  
<223> Xaa = S or C

<220>  
<221> VARIANT

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<222> 443  
 <223> Xaa = P or A

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 <222> 549  
 <223> Xaa = N or H

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 <223> Xaa = E or G

<220>  
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 <223> Xaa = K or R

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 <223> Xaa = K or N

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 <223> Xaa = G or E

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 1 5 10 15  
 Thr Leu Ser Leu Ala Arg Pro Ser Phe Ser Leu Val Glu Asp Xaa Thr  
 20 25 30  
 Leu Glu Pro Glu Glu Pro Pro Thr Lys Tyr Gln Ile Ser Gln Pro Glu  
 35 40 45  
 Val Tyr Val Ala Ala Pro Gly Glu Ser Leu Glu Val Arg Cys Leu Leu  
 50 55 60  
 Lys Asp Ala Ala Val Ile Ser Trp Thr Lys Asp Gly Val His Leu Gly  
 65 70 75 80  
 Pro Asn Asn Arg Thr Val Leu Ile Gly Glu Tyr Leu Gln Ile Lys Gly  
 85 90 95  
 Ala Thr Pro Arg Asp Ser Gly Leu Xaa Ala Cys Thr Ala Ser Arg Thr  
 100 105 110  
 Val Asp Ser Glu Thr Trp Tyr Phe Met Val Asn Val Thr Asp Ala Ile  
 115 120 125  
 Ser Ser Gly Asp Asp Glu Asp Asp Thr Asp Gly Ala Glu Asp Phe Val  
 130 135 140  
 Ser Glu Asn Ser Asn Asn Lys Xaa Ala Pro Tyr Trp Thr Asn Thr Glu  
 145 150 155 160  
 Lys Xaa Glu Lys Arg Leu His Ala Val Pro Ala Xaa Asn Thr Val Lys  
 165 170 175  
 Phe Arg Cys Pro Ala Gly Gly Asn Pro Xaa Pro Thr Met Arg Trp Leu  
 180 185 190  
 Lys Asn Gly Lys Glu Phe Lys Gln Glu His Arg Ile Gly Gly Tyr Lys  
 195 200 205  
 Val Arg Asn Gln His Trp Ser Leu Ile Met Glu Ser Val Val Pro Ser



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210	215	220
Asp Lys Gly Asn Tyr Thr Cys Val Val Glu Asn Glu Tyr Gly Ser Ile		
225	230	235
Asn His Thr Tyr His Leu Asp Val Val Glu Arg Xaa Xaa His Arg Pro		
	245	250
Ile Leu Gln Ala Gly Leu Pro Ala Asn Ala Xaa Thr Val Val Gly Gly		
	260	265
Asp Val Glu Xaa Val Xaa Lys Val Xaa Ser Asp Ala Gln Pro His Ile		
	275	280
Xaa Xaa Ile Lys His Val Glu Lys Asn Gly Ser Lys Tyr Gly Pro Asp		
	290	295
Gly Leu Pro Tyr Leu Lys Val Leu Lys Ala Xaa Gly Val Asn Thr Thr		
305	310	315
Asp Lys Glu Ile Glu Val Leu Tyr Ile Arg Asn Val Thr Phe Glu Asp		
	325	330
Ala Xaa Glu Xaa Xaa Xaa Leu Xaa Gly Asn Xaa Ile Gly Ile Xaa Phe		
	340	345
His Ser Ala Trp Leu Thr Val Leu Pro Ala Pro Gly Arg Glu Lys Glu		
	355	360
Ile Thr Ala Xaa Pro Asp Xaa Leu Glu Ile Ala Ile Tyr Cys Ile Xaa		
370	375	380
Val Phe Leu Ile Ala Cys Met Val Val Thr Val Ile Leu Cys Arg Met		
385	390	395
Lys Asn Thr Thr Lys Lys Pro Asp Phe Ser Ser Gln Pro Ala Val His		
	405	410
Lys Leu Thr Lys Arg Ile Pro Leu Arg Arg Gln Val Thr Val Ser Ala		
	420	425
Glu Ser Ser Ser Ser Met Asn Ser Asn Thr Xaa Leu Val Arg Ile Thr		
	435	440
Thr Arg Leu Ser Ser Thr Ala Asp Thr Pro Met Leu Ala Gly Val Ser		
450	455	460
Glu Tyr Glu Leu Pro Glu Asp Pro Lys Trp Glu Phe Pro Arg Asp Lys		
465	470	475
Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val Val		
	485	490
Met Ala Glu Ala Val Gly Ile Asp Lys Asp Lys Pro Lys Glu Ala Val		
	500	505
Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Glu Lys Asp Leu		
	515	520
Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile Gly Lys His		
530	535	540
Lys Asn Ile Ile Xaa Leu Leu Gly Ala Cys Thr Gln Asp Gly Pro Leu		
545	550	555
Tyr Val Ile Val Xaa Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr Leu		
	565	570
Arg Ala Arg Arg Pro Pro Gly Met Glu Tyr Ser Tyr Asp Ile Asn Arg		
	580	585
Val Pro Glu Glu Gln Met Thr Phe Lys Asp Leu Val Ser Cys Thr Tyr		
	595	600
Gln Leu Ala Arg Gly Met Glu Tyr Leu Ala Ser Gln Lys Cys Ile His		
	610	615
Arg Asp Leu Ala Ala Arg Asn Val Leu Val Thr Glu Asn Asn Val Met		
625	630	635
Xaa Ile Ala Asp Phe Gly Leu Ala Arg Asp Ile Asn Asn Ile Asp Tyr		
	645	650
Tyr Lys Xaa Thr Thr Asn Xaa Arg Leu Pro Val Lys Trp Met Ala Pro		

			660						665					670				
Glu	Ala	Leu	Phe	Asp	Xaa	Val	Tyr	Thr	His	Gln	Ser	Asp	Val	Trp	Ser			
			675						680					685				
Phe	Gly	Val	Leu	Met	Trp	Glu	Ile	Phe	Thr	Leu	Gly	Gly	Ser	Pro	Tyr			
			690						695					700				
Pro	Gly	Ile	Pro	Val	Glu	Glu	Leu	Phe	Lys	Leu	Leu	Lys	Glu	Gly	His			
705					710					715					720			
Arg	Met	Asp	Lys	Pro	Ala	Asn	Cys	Thr	Asn	Glu	Leu	Tyr	Met	Met	Met			
			725						730					735				
Arg	Asp	Cys	Trp	His	Ala	Val	Pro	Ser	Gln	Arg	Pro	Thr	Phe	Lys	Gln			
			740						745					750				
Leu	Val	Glu	Asp	Leu	Asp	Arg	Ile	Leu	Thr	Leu	Thr	Thr	Asn	Glu	Glu			
			755						760					765				
Tyr	Leu	Asp	Leu	Ser	Gln	Pro	Leu	Glu	Gln	Tyr	Ser	Pro	Ser	Tyr	Pro			
			770						775					780				
Asp	Thr	Arg	Ser	Ser	Cys	Ser	Ser	Gly	Asp	Asp	Ser	Val	Phe	Ser	Pro			
785					790					795					800			
Asp	Pro	Met	Pro	Tyr	Glu	Pro	Cys	Leu	Pro	Gln	Tyr	Pro	His	Ile	Asn			
			805						810					815				
Gly	Ser	Val	Lys	Thr														
			820															

```
<210> 302
<211> 806
<212> PRT
<213> Homo sapiens
```

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<220>  
<221> VARIANT  
<222> 65  
<223> Xaa = G or R
```

```
<220>  
<221> VARIANT  
<222> 250  
<223> Xaa = P or R
```

```
<220>  
<221> VARIANT  
<222> 383  
<223> Xaa = F or C
```

<400> 302																
Met	Gly	Ala	Pro	Ala	Cys	Ala	Leu	Ala	Leu	Cys	Val	Ala	Val	Ala	Ile	
1				5					10					15		
Val	Ala	Gly	Ala	Ser	Ser	Glu	Ser	Leu	Gly	Thr	Glu	Gln	Arg	Val	Val	
			20					25					30			
Gly	Arg	Ala	Ala	Glu	Val	Pro	Gly	Pro	Glu	Pro	Gly	Gln	Gln	Glu	Gln	
		35					40					45				
Leu	Val	Phe	Gly	Ser	Gly	Asp	Ala	Val	Glu	Leu	Ser	Cys	Pro	Pro	Pro	
	50					55					60					
Xaa	Gly	Gly	Pro	Met	Gly	Pro	Thr	Val	Trp	Val	Lys	Asp	Gly	Thr	Gly	
65					70					75					80	
Leu	Val	Pro	Ser	Glu	Arg	Val	Leu	Val	Gly	Pro	Gln	Arg	Leu	Gln	Val	
				85					90					95		

Leu	Asn	Ala	Ser	His	Glu	Asp	Ser	Gly	Ala	Tyr	Ser	Cys	Arg	Gln	Arg
			100					105					110		
Leu	Thr	Gln	Arg	Val	Leu	Cys	His	Phe	Ser	Val	Arg	Val	Thr	Asp	Ala
		115					120					125			
Pro	Ser	Ser	Gly	Asp	Asp	Glu	Asp	Gly	Glu	Asp	Glu	Ala	Glu	Asp	Thr
		130				135					140				
Gly	Val	Asp	Thr	Gly	Ala	Pro	Tyr	Trp	Thr	Arg	Pro	Glu	Arg	Met	Asp
145					150					155					160
Lys	Lys	Leu	Leu	Ala	Val	Pro	Ala	Ala	Asn	Thr	Val	Arg	Phe	Arg	Cys
				165					170					175	
Pro	Ala	Ala	Gly	Asn	Pro	Thr	Pro	Ser	Ile	Ser	Trp	Leu	Lys	Asn	Gly
			180					185					190		
Arg	Glu	Phe	Arg	Gly	Glu	His	Arg	Ile	Gly	Gly	Ile	Lys	Leu	Arg	His
		195					200					205			
Gln	Gln	Trp	Ser	Leu	Val	Met	Glu	Ser	Val	Val	Pro	Ser	Asp	Arg	Gly
		210				215					220				
Asn	Tyr	Thr	Cys	Val	Val	Glu	Asn	Lys	Phe	Gly	Ser	Ile	Arg	Gln	Thr
225				230						235					240
Tyr	Thr	Leu	Asp	Val	Leu	Glu	Arg	Ser	Xaa	His	Arg	Pro	Ile	Leu	Gln
				245					250					255	
Ala	Gly	Leu	Pro	Ala	Asn	Gln	Thr	Ala	Val	Leu	Gly	Ser	Asp	Val	Glu
			260					265					270		
Phe	His	Cys	Lys	Val	Tyr	Ser	Asp	Ala	Gln	Pro	His	Ile	Gln	Trp	Leu
		275					280					285			
Lys	His	Val	Glu	Val	Asn	Gly	Ser	Lys	Val	Gly	Pro	Asp	Gly	Thr	Pro
		290				295					300				
Tyr	Val	Thr	Val	Leu	Lys	Thr	Ala	Gly	Ala	Asn	Thr	Thr	Asp	Lys	Glu
305				310						315					320
Leu	Glu	Val	Leu	Ser	Leu	His	Asn	Val	Thr	Phe	Glu	Asp	Ala	Gly	Glu
				325					330					335	
Tyr	Thr	Cys	Leu	Ala	Gly	Asn	Ser	Ile	Gly	Phe	Ser	His	His	Ser	Ala
			340					345					350		
Trp	Leu	Val	Val	Leu	Pro	Ala	Glu	Glu	Glu	Leu	Val	Glu	Ala	Asp	Glu
		355					360					365			
Ala	Gly	Ser	Val	Tyr	Ala	Gly	Ile	Leu	Ser	Tyr	Gly	Val	Gly	Xaa	Phe
		370				375					380				
Leu	Phe	Ile	Leu	Val	Val	Ala	Ala	Val	Thr	Leu	Cys	Arg	Leu	Arg	Ser
385				390						395					400
Pro	Pro	Lys	Lys	Gly	Leu	Gly	Ser	Pro	Thr	Val	His	Lys	Ile	Ser	Arg
				405					410				415		
Phe	Pro	Leu	Lys	Arg	Gln	Val	Ser	Leu	Glu	Ser	Asn	Ala	Ser	Met	Ser
			420					425					430		
Ser	Asn	Thr	Pro	Leu	Val	Arg	Ile	Ala	Arg	Leu	Ser	Ser	Gly	Glu	Gly
			435				440					445			
Pro	Thr	Leu	Al												

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Cys Thr Gln Gly Gly Pro Leu Tyr Val Leu Val Glu Tyr Ala Ala Lys  
 545 550 555 560  
 Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg Pro Pro Gly Leu Asp  
 565 570 575  
 Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu Glu Gln Leu Thr Phe Lys  
 580 585 590  
 Asp Leu Val Ser Cys Ala Tyr Gln Val Ala Arg Gly Met Glu Tyr Leu  
 595 600 605  
 Ala Ser Gln Lys Cys Ile His Arg Asp Leu Ala Ala Arg Asn Val Leu  
 610 615 620  
 Val Thr Glu Asp Asn Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg  
 625 630 635 640  
 Asp Val His Asn Leu Asp Tyr Tyr Lys Lys Thr Thr Asn Gly Arg Leu  
 645 650 655  
 Pro Val Lys Trp Met Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr  
 660 665 670  
 His Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe  
 675 680 685  
 Thr Leu Gly Gly Ser Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe  
 690 695 700  
 Lys Leu Leu Lys Glu Gly His Arg Met Asp Lys Pro Ala Asn Cys Thr  
 705 710 715 720  
 His Asp Leu Tyr Met Ile Met Arg Glu Cys Trp His Ala Ala Pro Ser  
 725 730 735  
 Gln Arg Pro Thr Phe Lys Gln Leu Val Glu Asp Leu Asp Arg Val Leu  
 740 745 750  
 Thr Val Thr Ser Thr Asp Glu Tyr Leu Asp Leu Ser Ala Pro Phe Glu  
 755 760 765  
 Gln Tyr Ser Pro Gly Gly Gln Asp Thr Pro Ser Ser Ser Ser Gly  
 770 775 780  
 Asp Asp Ser Val Phe Ala His Asp Leu Leu Pro Pro Ala Pro Pro Ser  
 785 790 795 800  
 Ser Gly Gly Ser Arg Thr  
 805

<210> 303  
 <211> 802  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 10  
 <223> Xaa = V or I

<220>  
 <221> VARIANT  
 <222> 136  
 <223> Xaa = P or L

<220>  
 <221> VARIANT  
 <222> 275  
 <223> Xaa = S or R

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<220>  
 <221> VARIANT  
 <222> 297  
 <223> Xaa = D or V

<220>  
 <221> VARIANT  
 <222> 388  
 <223> Xaa = G or R

<220>  
 <221> VARIANT  
 <222> 616  
 <223> Xaa = R or L

<400> 303  
 Met Arg Leu Leu Ala Leu Leu Gly Xaa Leu Leu Ser Val Pro Gly  
 1 5 10 15  
 Pro Pro Val Leu Ser Leu Glu Ala Ser Glu Glu Val Glu Leu Glu Pro  
 20 25 30  
 Cys Leu Ala Pro Ser Leu Glu Gln Gln Glu Leu Thr Val Ala  
 35 40 45  
 Leu Gly Gln Pro Val Arg Leu Cys Cys Gly Arg Ala Glu Arg Gly Gly  
 50 55 60  
 His Trp Tyr Lys Glu Gly Ser Arg Leu Ala Pro Ala Gly Arg Val Arg  
 65 70 75 80  
 Gly Trp Arg Gly Arg Leu Glu Ile Ala Ser Phe Leu Pro Glu Asp Ala  
 85 90 95  
 Gly Arg Tyr Leu Cys Leu Ala Arg Gly Ser Met Ile Val Leu Gln Asn  
 100 105 110  
 Leu Thr Leu Ile Thr Gly Asp Ser Leu Thr Ser Ser Asn Asp Asp Glu  
 115 120 125  
 Asp Pro Lys Ser His Arg Asp Xaa Ser Asn Arg His Ser Tyr Pro Gln  
 130 135 140  
 Gln Ala Pro Tyr Trp Thr His Pro Gln Arg Met Glu Lys Lys Leu His  
 145 150 155 160  
 Ala Val Pro Ala Gly Asn Thr Val Lys Phe Arg Cys Pro Ala Ala Gly  
 165 170 175  
 Asn Pro Thr Pro Thr Ile Arg Trp Leu Lys Asp Gly Gln Ala Phe His  
 180 185 190  
 Gly Glu Asn Arg Ile Gly Gly Ile Arg Leu Arg His Gln His Trp Ser  
 195 200 205  
 Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly Thr Tyr Thr Cys  
 210 215 220  
 Leu Val Glu Asn Ala Val Gly Ser Ile Arg Tyr Asn Tyr Leu Leu Asp  
 225 230 235 240  
 Val Leu Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro  
 245 250 255  
 Ala Asn Thr Thr Ala Val Val Gly Ser Asp Val Glu Leu Leu Cys Lys  
 260 265 270  
 Val Tyr Xaa Asp Ala Gln Pro His Ile Gln Trp Leu Lys His Ile Val  
 275 280 285  
 Ile Asn Gly Ser Ser Phe Gly Ala Xaa Gly Phe Pro Tyr Val Gln Val  
 290 295 300  
 Leu Lys Thr Ala Asp Ile Asn Ser Ser Glu Val Glu Val Leu Tyr Leu  
 305 310 315 320

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Arg Asn Val Ser Ala Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly  
 325 330 335  
 Asn Ser Ile Gly Leu Ser Tyr Gln Ser Ala Trp Leu Thr Val Leu Pro  
 340 345 350  
 Glu Glu Asp Pro Thr Trp Thr Ala Ala Ala Pro Glu Ala Arg Tyr Thr  
 355 360 365  
 Asp Ile Ile Leu Tyr Ala Ser Gly Ser Leu Ala Leu Ala Val Leu Leu  
 370 375 380  
 Leu Leu Ala Xaa Leu Tyr Arg Gly Gln Ala Leu His Gly Arg His Pro  
 385 390 395 400  
 Arg Pro Pro Ala Thr Val Gln Lys Leu Ser Arg Phe Pro Leu Ala Arg  
 405 410 415  
 Gln Phe Ser Leu Glu Ser Gly Ser Ser Gly Lys Ser Ser Ser Ser Leu  
 420 425 430  
 Val Arg Gly Val Arg Leu Ser Ser Ser Gly Pro Ala Leu Leu Ala Gly  
 435 440 445  
 Leu Val Ser Leu Asp Leu Pro Leu Asp Pro Leu Trp Glu Phe Pro Arg  
 450 455 460  
 Asp Arg Leu Val Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln  
 465 470 475 480  
 Val Val Arg Ala Glu Ala Phe Gly Met Asp Pro Ala Arg Pro Asp Gln  
 485 490 495  
 Ala Ser Thr Val Ala Val Lys Met Leu Lys Asp Asn Ala Ser Asp Lys  
 500 505 510  
 Asp Leu Ala Asp Leu Val Ser Glu Met Glu Val Met Lys Leu Ile Gly  
 515 520 525  
 Arg His Lys Asn Ile Ile Asn Leu Leu Gly Val Cys Thr Gln Glu Gly  
 530 535 540  
 Pro Leu Tyr Val Ile Val Glu Cys Ala Ala Lys Gly Asn Leu Arg Glu  
 545 550 555 560  
 Phe Leu Arg Ala Arg Arg Pro Pro Gly Pro Asp Leu Ser Pro Asp Gly  
 565 570 575  
 Pro Arg Ser Ser Glu Gly Pro Leu Ser Phe Pro Val Leu Val Ser Cys  
 580 585 590  
 Ala Tyr Gln Val Ala Arg Gly Met Gln Tyr Leu Glu Ser Arg Lys Cys  
 595 600 605  
 Ile His Arg Asp Leu Ala Ala Xaa Asn Val Leu Val Thr Glu Asp Asn  
 610 615 620  
 Val Met Lys Ile Ala Asp Phe Gly Leu Ala Arg Gly Val His His Ile  
 625 630 635 640  
 Asp Tyr Tyr Lys Lys Thr Ser Asn Gly Arg Leu Pro Val Lys Trp Met  
 645 650 655  
 Ala Pro Glu Ala Leu Phe Asp Arg Val Tyr Thr His Gln Ser Asp Val  
 660 665 670  
 Trp Ser Phe Gly Ile Leu Leu Trp Glu Ile Phe Thr Leu Gly Gly Ser  
 675 680 685  
 Pro Tyr Pro Gly Ile Pro Val Glu Glu Leu Phe Ser Leu Leu Arg Glu  
 690 695 700  
 Gly His Arg Met Asp Arg Pro Pro His Cys Pro Pro Glu Leu Tyr Gly  
 705 710 715 720  
 Leu Met Arg Glu Cys Trp His Ala Ala Pro Ser Gln Arg Pro Thr Phe  
 725 730 735  
 Lys Gln Leu Val Glu Ala Leu Asp Lys Val Leu Leu Ala Val Ser Glu  
 740 745 750  
 Glu Tyr Leu Asp Leu Arg Leu Thr Phe Gly Pro Tyr Ser Pro Ser Gly  
 755 760 765

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Gly Asp Ala Ser Ser Thr Cys Ser Ser Ser Asp Ser Val Phe Ser His  
 770 775 780  
 Asp Pro Leu Pro Leu Gly Ser Ser Ser Phe Pro Phe Gly Ser Gly Val  
 785 790 795 800  
 Gln Thr

<210> 304  
 <211> 993  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 835  
 <223> Xaa = D or Y or H or F

<220>  
 <221> VARIANT  
 <222> 836  
 <223> Xaa = I or S

<220>  
 <221> VARIANT  
 <222> 841  
 <223> Xaa = N or I

<220>  
 <221> VARIANT  
 <222> 842  
 <223> Xaa = Y or H

<400> 304  
 Met Pro Ala Leu Ala Arg Asp Ala Gly Thr Val Pro Leu Leu Val Val  
 1 5 10 15  
 Phe Ser Ala Met Ile Phe Gly Thr Ile Thr Asn Gln Asp Leu Pro Val  
 20 25 30  
 Ile Lys Cys Val Leu Ile Asn His Lys Asn Asn Asp Ser Ser Val Gly  
 35 40 45  
 Lys Ser Ser Ser Tyr Pro Met Val Ser Glu Ser Pro Glu Asp Leu Gly  
 50 55 60  
 Cys Ala Leu Arg Pro Gln Ser Ser Gly Thr Val Tyr Glu Ala Ala Ala  
 65 70 75 80  
 Val Glu Val Asp Val Ser Ala Ser Ile Thr Leu Gln Val Leu Val Asp  
 85 90 95  
 Ala Pro Gly Asn Ile Ser Cys Leu Trp Val Phe Lys His Ser Ser Leu  
 100 105 110  
 Asn Cys Gln Pro His Phe Asp Leu Gln Asn Arg Gly Val Val Ser Met  
 115 120 125  
 Val Ile Leu Lys Met Thr Glu Thr Gln Ala Gly Glu Tyr Leu Leu Phe  
 130 135 140  
 Ile Gln Ser Glu Ala Thr Asn Tyr Thr Ile Leu Phe Thr Val Ser Ile  
 145 150 155 160  
 Arg Asn Thr Leu Leu Tyr Thr Leu Arg Arg Pro Tyr Phe Arg Lys Met  
 165 170 175

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Glu	Asn	Gln	Asp	Ala	Leu	Val	Cys	Ile	Ser	Glu	Ser	Val	Pro	Glu	Pro
			180					185					190		
Ile	Val	Glu	Trp	Val	Leu	Cys	Asp	Ser	Gln	Gly	Glu	Ser	Cys	Lys	Glu
		195					200					205			
Glu	Ser	Pro	Ala	Val	Val	Lys	Lys	Glu	Glu	Lys	Val	Leu	His	Glu	Leu
		210				215					220				
Phe	Gly	Thr	Asp	Ile	Arg	Cys	Cys	Ala	Arg	Asn	Glu	Leu	Gly	Arg	Glu
225				230						235				240	
Cys	Thr	Arg	Leu	Phe	Thr	Ile	Asp	Leu	Asn	Gln	Thr	Pro	Gln	Thr	Thr
			245					250					255		
Leu	Pro	Gln	Leu	Phe	Leu	Lys	Val	Gly	Glu	Pro	Leu	Trp	Ile	Arg	Cys
		260						265					270		
Lys	Ala	Val	His	Val	Asn	His	Gly	Phe	Gly	Leu	Thr	Trp	Glu	Leu	Glu
		275					280					285			
Asn	Lys	Ala	Leu	Glu	Glu	Gly	Asn	Tyr	Phe	Glu	Met	Ser	Thr	Tyr	Ser
		290				295					300				
Thr	Asn	Arg	Thr	Met	Ile	Arg	Ile	Leu	Phe	Ala	Phe	Val	Ser	Ser	Val
305				310						315					320
Ala	Arg	Asn	Asp	Thr	Gly	Tyr	Tyr	Thr	Cys	Ser	Ser	Ser	Lys	His	Pro
			325						330					335	
Ser	Gln	Ser	Ala	Leu	Val	Thr	Ile	Val	Gly	Lys	Gly	Phe	Ile	Asn	Ala
			340					345					350		
Thr	Asn	Ser	Ser	Glu	Asp	Tyr	Glu	Ile	Asp	Gln	Tyr	Glu	Glu	Phe	Cys
		355					360					365			
Phe	Ser	Val	Arg	Phe	Lys	Ala	Tyr	Pro	Gln	Ile	Arg	Cys	Thr	Trp	Thr
		370				375					380				
Phe	Ser	Arg	Lys	Ser	Phe	Pro	Cys	Glu	Gln	Lys	Gly	Leu	Asp	Asn	Gly
385				390						395				400	
Tyr	Ser	Ile	Ser	Lys	Phe	Cys	Asn	His	Lys	His	Gln	Pro	Gly	Glu	Tyr
				405					410					415	
Ile	Phe	His	Ala	Glu	Asn	Asp	Asp	Ala	Gln	Phe	Thr	Lys	Met	Phe	Thr
			420					425					430		
Leu	Asn	Ile	Arg	Arg	Lys	Pro	Gln	Val	Leu	Ala	Glu	Ala	Ser	Ala	Ser
		435					440					445			
Gln	Ala	Ser	Cys	Phe	Ser	Asp	Gly	Tyr	Pro	Leu	Pro	Ser	Trp	Thr	Trp
		450				455					460				
Lys	Lys	Cys	Ser	Asp	Lys	Ser	Pro	Asn	Cys	Thr	Glu	Glu	Ile	Thr	Glu
465				470					475					480	
Gly	Val	Trp	Asn	Arg	Lys	Ala	Asn	Arg	Lys	Val	Phe	Gly	Gln	Trp	Val
			485					490					495		
Ser	Ser	Ser	Thr	Leu	Asn	Met	Ser	Glu	Ala	Ile	Lys	Gly	Phe	Leu	Val
			500					505					510		
Lys	Cys	Cys	Ala	Tyr	Asn	Ser	Leu	Gly	Thr	Ser	Cys	Glu	Thr	Ile	Leu
		515					520					525			
Leu	Asn	Ser	Pro	Gly	Pro	Phe	Pro	Phe	Ile	Gln	Asp	Asn	Ile	Ser	Phe
		530				535					540				
Tyr	Ala	Thr	Ile	Gly	Val	Cys	Leu	Leu	Phe	Ile	Val	Val	Leu	Thr	Leu
545				550						555					560
Leu	Ile	Cys	His	Lys	Tyr	Lys	Lys	Gln	Phe	Arg	Tyr	Glu	Ser	Gln	Leu
			565						570					575	
Gln	Met	Val	Gln	Val	Thr	Gly	Ser	Ser	Asp	Asn	Glu	Tyr	Phe	Tyr	Val
			580					585					590		
Asp	Phe	Arg	Glu	Tyr	Glu	Tyr	Asp	Leu	Lys	Trp	Glu	Phe	Pro	Arg	Glu
		595					600					605			
Asn	Leu	Glu	Phe	Gly	Lys	Val	Leu	Gly	Ser	Gly	Ala	Phe	Gly	Lys	Val
		610				615					620				



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Met Asn Ala Thr Ala Tyr Gly Ile Ser Lys Thr Gly Val Ser Ile Gln
625          630          635          640
Val Ala Val Lys Met Leu Lys Glu Lys Ala Asp Ser Ser Glu Arg Glu
          645          650          655
Ala Leu Met Ser Glu Leu Lys Met Met Thr Gln Leu Gly Ser His Glu
          660          665          670
Asn Ile Val Asn Leu Leu Gly Ala Cys Thr Leu Ser Gly Pro Ile Tyr
          675          680          685
Leu Ile Phe Glu Tyr Cys Cys Tyr Gly Asp Leu Leu Asn Tyr Leu Arg
          690          695          700
Ser Lys Arg Glu Lys Phe His Arg Thr Trp Thr Glu Ile Phe Lys Glu
705          710          715          720
His Asn Phe Ser Phe Tyr Pro Thr Phe Gln Ser His Pro Asn Ser Ser
          725          730          735
Met Pro Gly Ser Arg Glu Val Gln Ile His Pro Asp Ser Asp Gln Ile
          740          745          750
Ser Gly Leu His Gly Asn Ser Phe His Ser Glu Asp Glu Ile Glu Tyr
          755          760          765
Glu Asn Gln Lys Arg Leu Glu Glu Glu Glu Asp Leu Asn Val Leu Thr
          770          775          780
Phe Glu Asp Leu Leu Cys Phe Ala Tyr Gln Val Ala Lys Gly Met Glu
785          790          795          800
Phe Leu Glu Phe Lys Ser Cys Val His Arg Asp Leu Ala Ala Arg Asn
          805          810          815
Val Leu Val Thr His Gly Lys Val Val Lys Ile Cys Asp Phe Gly Leu
          820          825          830
Ala Arg Xaa Xaa Met Ser Asp Ser Xaa Xaa Val Val Arg Gly Asn Ala
          835          840          845
Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ser Leu Phe Glu Gly Ile
          850          855          860
Tyr Thr Ile Lys Ser Asp Val Trp Ser Tyr Gly Ile Leu Leu Trp Glu
865          870          875          880
Ile Phe Ser Leu Gly Val Asn Pro Tyr Pro Gly Ile Pro Val Asp Ala
          885          890          895
Asn Phe Tyr Lys Leu Ile Gln Asn Gly Phe Lys Met Asp Gln Pro Phe
          900          905          910
Tyr Ala Thr Glu Glu Ile Tyr Ile Ile Met Gln Ser Cys Trp Ala Phe
          915          920          925
Asp Ser Arg Lys Arg Pro Ser Phe Pro Asn Leu Thr Ser Phe Leu Gly
          930          935          940
Cys Gln Leu Ala Asp Ala Glu Glu Ala Met Tyr Gln Asn Val Asp Gly
945          950          955          960
Arg Val Ser Glu Cys Pro His Thr Tyr Gln Asn Arg Arg Pro Phe Ser
          965          970          975
Arg Glu Met Asp Leu Gly Leu Leu Ser Pro Gln Ala Gln Val Glu Asp
          980          985          990
Ser

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&lt;210&gt; 305

&lt;211&gt; 976

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

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<221> VARIANT  
<222> 541  
<223> Xaa = M or L or V

<220>  
<221> VARIANT  
<222> 557  
<223> Xaa = W or R

<220>  
<221> VARIANT  
<222> 664  
<223> Xaa = G or R

<220>  
<221> VARIANT  
<222> 788, 136  
<223> Xaa = C or R

<220>  
<221> VARIANT  
<222> 802  
<223> Xaa = T or I

<220>  
<221> VARIANT  
<222> 816, 820  
<223> Xaa = D or V or H or Y

<220>  
<221> VARIANT  
<222> 822  
<223> Xaa = N or Y or K

<220>  
<221> VARIANT  
<222> 823  
<223> Xaa = Y or D or C

<220>  
<221> VARIANT  
<222> 835  
<223> Xaa = W or R

<220>  
<221> VARIANT  
<222> 869  
<223> Xaa = P or S

<220>  
<221> VARIANT  
<222> 900  
<223> Xaa = Y or F

<220>  
<221> VARIANT

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&lt;222&gt; 52

&lt;223&gt; Xaa = D or N

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 178

&lt;223&gt; Xaa = A or T

&lt;400&gt; 305

```

Met Arg Gly Ala Arg Gly Ala Trp Asp Phe Leu Cys Val Leu Leu Leu
 1           5           10           15
Leu Leu Arg Val Gln Thr Gly Ser Ser Gln Pro Ser Val Ser Pro Gly
      20           25           30
Glu Pro Ser Pro Pro Ser Ile His Pro Gly Lys Ser Asp Leu Ile Val
      35           40           45
Arg Val Gly Xaa Glu Ile Arg Leu Leu Cys Thr Asp Pro Gly Phe Val
      50           55           60
Lys Trp Thr Phe Glu Ile Leu Asp Glu Thr Asn Glu Asn Lys Gln Asn
      65           70           75           80
Glu Trp Ile Thr Glu Lys Ala Glu Ala Thr Asn Thr Gly Lys Tyr Thr
      85           90           95
Cys Thr Asn Lys His Gly Leu Ser Asn Ser Ile Tyr Val Phe Val Arg
      100           105           110
Asp Pro Ala Lys Leu Phe Leu Val Asp Arg Ser Leu Tyr Gly Lys Glu
      115           120           125
Asp Asn Asp Thr Leu Val Arg Xaa Pro Leu Thr Asp Pro Glu Val Thr
      130           135           140
Asn Tyr Ser Leu Lys Gly Cys Gln Gly Lys Pro Leu Pro Lys Asp Leu
      145           150           155           160
Arg Phe Ile Pro Asp Pro Lys Ala Gly Ile Met Ile Lys Ser Val Lys
      165           170           175
Arg Xaa Tyr His Arg Leu Cys Leu His Cys Ser Val Asp Gln Glu Gly
      180           185           190
Lys Ser Val Leu Ser Glu Lys Phe Ile Leu Lys Val Arg Pro Ala Phe
      195           200           205
Lys Ala Val Pro Val Val Ser Val Ser Lys Ala Ser Tyr Leu Leu Arg
      210           215           220
Glu Gly Glu Glu Phe Thr Val Thr Cys Thr Ile Lys Asp Val Ser Ser
      225           230           235           240
Ser Val Tyr Ser Thr Trp Lys Arg Glu Asn Ser Gln Thr Lys Leu Gln
      245           250           255
Glu Lys Tyr Asn Ser Trp His His Gly Asp Phe Asn Tyr Glu Arg Gln
      260           265           270
Ala Thr Leu Thr Ile Ser Ser Ala Arg Val Asn Asp Ser Gly Val Phe
      275           280           285
Met Cys Tyr Ala Asn Asn Thr Phe Gly Ser Ala Asn Val Thr Thr Thr
      290           295           300
Leu Glu Val Val Asp Lys Gly Phe Ile Asn Ile Phe Pro Met Ile Asn
      305           310           315           320
Thr Thr Val Phe Val Asn Asp Gly Glu Asn Val Asp Leu Ile Val Glu
      325           330           335
Tyr Glu Ala Phe Pro Lys Pro Glu His Gln Gln Trp Ile Tyr Met Asn
      340           345           350
Arg Thr Phe Thr Asp Lys Trp Glu Asp Tyr Pro Lys Ser Glu Asn Glu
      355           360           365
Ser Asn Ile Arg Tyr Val Ser Glu Leu His Leu Thr Arg Leu Lys Gly

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370	375	380
Thr Glu Gly Gly Thr Tyr Thr Phe Leu Val Ser Asn Ser Asp Val Asn		
385	390	395
Ala Ala Ile Ala Phe Asn Val Tyr Val Asn Thr Lys Pro Glu Ile Leu		
	405	410
Thr Tyr Asp Arg Leu Val Asn Gly Met Leu Gln Cys Val Ala Ala Gly		
	420	425
Phe Pro Glu Pro Thr Ile Asp Trp Tyr Phe Cys Pro Gly Thr Glu Gln		
	435	440
Arg Cys Ser Ala Ser Val Leu Pro Val Asp Val Gln Thr Leu Asn Ser		
	450	455
Ser Gly Pro Pro Phe Gly Lys Leu Val Val Gln Ser Ser Ile Asp Ser		
465	470	475
Ser Ala Phe Lys His Asn Gly Thr Val Glu Cys Lys Ala Tyr Asn Asp		
	485	490
Val Gly Lys Thr Ser Ala Tyr Phe Asn Phe Ala Phe Lys Gly Asn Asn		
	500	505
Lys Glu Gln Ile His Pro His Thr Leu Phe Thr Pro Leu Leu Ile Gly		
	515	520
Phe Val Ile Val Ala Gly Met Met Cys Ile Ile Val Xaa Ile Leu Thr		
	530	535
Tyr Lys Tyr Leu Gln Lys Pro Met Tyr Glu Val Gln Xaa Lys Val Val		
545	550	555
Glu Glu Ile Asn Gly Asn Asn Tyr Val Tyr Ile Asp Pro Thr Gln Leu		
	565	570
Pro Tyr Asp His Lys Trp Glu Phe Pro Arg Asn Arg Leu Ser Phe Gly		
	580	585
Lys Thr Leu Gly Ala Gly Ala Phe Gly Lys Val Val Glu Ala Thr Ala		
	595	600
Tyr Gly Leu Ile Lys Ser Asp Ala Ala Met Thr Val Ala Val Lys Met		
	610	615
Leu Lys Pro Ser Ala His Leu Thr Glu Arg Glu Ala Leu Met Ser Glu		
625	630	635
Leu Lys Val Leu Ser Tyr Leu Gly Asn His Met Asn Ile Val Asn Leu		
	645	650
Leu Gly Ala Cys Thr Ile Gly Xaa Pro Thr Leu Val Ile Thr Glu Tyr		
	660	665
Cys Cys Tyr Gly Asp Leu Leu Asn Phe Leu Arg Arg Lys Arg Asp Ser		
	675	680
Phe Ile Cys Ser Lys Gln Glu Asp His Ala Glu Ala Ala Leu Tyr Lys		
	690	695
Asn Leu Leu His Ser Lys Glu Ser Ser Cys Ser Asp Ser Thr Asn Glu		
705	710	715
Tyr Met Asp Met Lys Pro Gly Val Ser Tyr Val Val Pro Thr Lys Ala		
	725	730
Asp Lys Arg Arg Ser Val Arg Ile Gly Ser Tyr Ile Glu Arg Asp Val		
	740	745
Thr Pro Ala Ile Met Glu Asp Asp Glu Leu Ala Leu Asp Leu Glu Asp		
	755	760
Leu Leu Ser Phe Ser Tyr Gln Val Ala Lys Gly Met Ala Phe Leu Ala		
	770	775
Ser Lys Asn Xaa Ile His Arg Asp Leu Ala Ala Arg Asn Ile Leu Leu		
785	790	795
Xaa His Gly Arg Ile Thr Lys Ile Cys Asp Phe Gly Leu Ala Arg Xaa		
	805	810
Ile Lys Asn Xaa Ser Xaa Xaa Val Val Lys Gly Asn Ala Arg Leu Pro		
		815

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			820					825					830				
Val	Lys	Xaa	Met	Ala	Pro	Glu	Ser	Ile	Phe	Asn	Cys	Val	Tyr	Thr	Phe		
		835						840					845				
Glu	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Ile	Phe	Leu	Trp	Glu	Leu	Phe	Ser		
		850					855					860					
Leu	Gly	Ser	Ser	Xaa	Tyr	Pro	Gly	Met	Pro	Val	Asp	Ser	Lys	Phe	Tyr		
865					870					875					880		
Lys	Met	Ile	Lys	Glu	Gly	Phe	Arg	Met	Leu	Ser	Pro	Glu	His	Ala	Pro		
				885					890					895			
Ala	Glu	Met	Xaa	Asp	Ile	Met	Lys	Thr	Cys	Trp	Asp	Ala	Asp	Pro	Leu		
			900					905					910				
Lys	Arg	Pro	Thr	Phe	Lys	Gln	Ile	Val	Gln	Leu	Ile	Glu	Lys	Gln	Ile		
		915					920					925					
Ser	Glu	Ser	Thr	Asn	His	Ile	Tyr	Ser	Asn	Leu	Ala	Asn	Cys	Ser	Pro		
		930				935					940						
Asn	Arg	Gln	Lys	Pro	Val	Val	Asp	His	Ser	Val	Arg	Ile	Asn	Ser	Val		
945				950					955						960		
Gly	Ser	Thr	Ala	Ser	Ser	Ser	Gln	Pro	Leu	Leu	Val	His	Asp	Asp	Val		
				965					970					975			

&lt;210&gt; 306

&lt;211&gt; 1390

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 37, 145, 158, 237

&lt;223&gt; Xaa = V or A

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 39, 1250

&lt;223&gt; Xaa = M or T

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 42

&lt;223&gt; Xaa = Q or R

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 113, 508

&lt;223&gt; Xaa = K or R

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 114, 382

&lt;223&gt; Xaa = D or N

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 148, 476, 1094

&lt;223&gt; Xaa = H or R

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<220>  
<221> VARIANT  
<222> 151  
<223> Xaa = T or P

<220>  
<221> VARIANT  
<222> 168  
<223> Xaa = E or D

<220>  
<221> VARIANT  
<222> 193  
<223> Xaa = I or T

<220>  
<221> VARIANT  
<222> 216  
<223> Xaa = V or L

<220>  
<221> VARIANT  
<222> 276, 511, 729  
<223> Xaa = T or A

<220>  
<221> VARIANT  
<222> 314  
<223> Xaa = F or L

<220>  
<221> VARIANT  
<222> 337  
<223> Xaa = L or P

<220>  
<221> VARIANT  
<222> 340  
<223> Xaa = D or V

<220>  
<221> VARIANT  
<222> 400  
<223> Xaa = R or G

<220>  
<221> VARIANT  
<222> 481  
<223> Xaa = L or M

<220>  
<221> VARIANT  
<222> 500  
<223> Xaa = D or G

<220>

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<221> VARIANT  
 <222> 501, 542  
 <223> Xaa = Y or H

<220>  
 <221> VARIANT  
 <222> 622  
 <223> Xaa = L or S

<220>  
 <221> VARIANT  
 <222> 720  
 <223> Xaa = F or S

<220>  
 <221> VARIANT  
 <222> 1100  
 <223> Xaa = N or Y

<220>  
 <221> VARIANT  
 <222> 1230  
 <223> Xaa = C or Y

<220>  
 <221> VARIANT  
 <222> 1235  
 <223> Xaa = Y or D

<400> 306  
 Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe  
 1 5 10 15  
 Thr Leu Val Gln Arg Ser Asn Gly Glu Cys Lys Glu Ala Leu Ala Lys  
 20 25 30  
 Ser Glu Met Asn Xaa Asn Xaa Lys Tyr Xaa Leu Pro Asn Phe Thr Ala  
 35 40 45  
 Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu  
 50 55 60  
 Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys  
 65 70 75 80  
 Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe  
 85 90 95  
 Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp  
 100 105 110  
 Xaa Xaa Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp  
 115 120 125  
 Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His  
 130 135 140  
 Xaa Phe Pro Xaa Asn His Xaa Ala Asp Ile Gln Ser Glu Xaa His Cys  
 145 150 155 160  
 Ile Phe Ser Pro Gln Ile Glu Xaa Pro Ser Gln Cys Pro Asp Cys Val  
 165 170 175  
 Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe  
 180 185 190  
 Xaa Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp  
 195 200 205

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His	Pro	Leu	His	Ser	Ile	Ser	Xaa	Arg	Arg	Leu	Lys	Glu	Thr	Lys	Asp
	210					215					220				
Gly	Phe	Met	Phe	Leu	Thr	Asp	Gln	Ser	Tyr	Ile	Asp	Xaa	Leu	Pro	Glu
225					230					235					240
Phe	Arg	Asp	Ser	Tyr	Pro	Ile	Lys	Tyr	Val	His	Ala	Phe	Glu	Ser	Asn
			245					250						255	
Asn	Phe	Ile	Tyr	Phe	Leu	Thr	Val	Gln	Arg	Glu	Thr	Leu	Asp	Ala	Gln
		260					265					270			
Thr	Phe	His	Xaa	Arg	Ile	Ile	Arg	Phe	Cys	Ser	Ile	Asn	Ser	Gly	Leu
	275					280					285				
His	Ser	Tyr	Met	Glu	Met	Pro	Leu	Glu	Cys	Ile	Leu	Thr	Glu	Lys	Arg
	290					295				300					
Lys	Lys	Arg	Ser	Thr	Lys	Lys	Glu	Val	Xaa	Asn	Ile	Leu	Gln	Ala	Ala
305					310					315					320
Tyr	Val	Ser	Lys	Pro	Gly	Ala	Gln	Leu	Ala	Arg	Gln	Ile	Gly	Ala	Ser
			325						330					335	
Xaa	Asn	Asp	Xaa	Ile	Leu	Phe	Gly	Val	Phe	Ala	Gln	Ser	Lys	Pro	Asp
		340					345						350		
Ser	Ala	Glu	Pro	Met	Asp	Arg	Ser	Ala	Met	Cys	Ala	Phe	Pro	Ile	Lys
	355					360						365			
Tyr	Val	Asn	Asp	Phe	Phe	Asn	Lys	Ile	Val	Asn	Lys	Asn	Xaa	Val	Arg
	370					375				380					
Cys	Leu	Gln	His	Phe	Tyr	Gly	Pro	Asn	His	Glu	His	Cys	Phe	Asn	Xaa
385					390					395					400
Thr	Leu	Leu	Arg	Asn	Ser	Ser	Gly	Cys	Glu	Ala	Arg	Arg	Asp	Glu	Tyr
			405					410					415		
Arg	Thr	Glu	Phe	Thr	Thr	Ala	Leu	Gln	Arg	Val	Asp	Leu	Phe	Met	Gly
		420					425					430			
Gln	Phe	Ser	Glu	Val	Leu	Leu	Thr	Ser	Ile	Ser	Thr	Phe	Ile	Lys	Gly
	435						440					445			
Asp	Leu	Thr	Ile	Ala	Asn	Leu	Gly	Thr	Ser	Glu	Gly	Arg	Phe	Met	Gln
	450					455				460					
Val	Val	Val	Ser	Arg	Ser	Gly	Pro	Ser	Thr	Pro	Xaa	Val	Asn	Phe	Leu
465					470					475					480
Xaa	Asp	Ser	His	Pro	Val	Ser	Pro	Glu	Val	Ile	Val	Glu	His	Thr	Leu
			485					490						495	
Asn	Gln	Asn	Xaa	Xaa	Thr	Leu	Val	Ile	Thr	Gly	Xaa	Lys	Ile	Xaa	Lys
		500						505					510		
Ile	Pro	Leu	Asn	Gly	Leu	Gly	Cys	Arg	His	Phe	Gln	Ser	Cys	Ser	Gln
		515					520					525			
Cys	Leu	Ser	Ala	Pro	Pro	Phe	Val	Gln	Cys	Gly	Trp	Cys	Xaa	Asp	Lys
	530					535				540					
Cys	Val	Arg	Ser	Glu	Glu	Cys	Leu	Ser	Gly	Thr	Trp	Thr	Gln	Gln	Ile
545					550					555					560
Cys	Leu	Pro	Ala	Ile	Tyr	Lys	Val	Phe	Pro	Asn	Ser	Ala	Pro	Leu	Glu
			565					570					575		
Gly	Gly	Thr	Arg	Leu	Thr	Ile	Cys	Gly	Trp	Asp	Phe	Gly	Phe	Arg	Arg
		580					585					590			
Asn	Asn	Lys	Phe	Asp	Leu	Lys	Lys	Thr	Arg	Val	Leu	Leu	Gly	Asn	Glu
		595					600					605			
Ser	Cys	Thr	Leu	Thr	Leu	Ser	Glu	Ser	Thr	Met	Asn	Thr	Xaa	Lys	Cys
	610					615					620				
Thr	Val	Gly	Pro	Ala	Met	Asn	Lys	His	Phe	Asn	Met	Ser	Ile	Ile	Ile
625					630					635					640
Ser	Asn	Gly	His	Gly	Thr	Thr	Gln	Tyr	Ser	Thr	Phe	Ser	Tyr	Val	Asp
			645						650					655	



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Pro	Val	Ile	Thr	Ser	Ile	Ser	Pro	Lys	Tyr	Gly	Pro	Met	Ala	Gly	Gly
			660					665					670		
Thr	Leu	Leu	Thr	Leu	Thr	Gly	Asn	Tyr	Leu	Asn	Ser	Gly	Asn	Ser	Arg
		675					680					685			
His	Ile	Ser	Ile	Gly	Gly	Lys	Thr	Cys	Thr	Leu	Lys	Ser	Val	Ser	Asn
	690					695					700				
Ser	Ile	Leu	Glu	Cys	Tyr	Thr	Pro	Ala	Gln	Thr	Ile	Ser	Thr	Glu	Xaa
705					710					715					720
Ala	Val	Lys	Leu	Lys	Ile	Asp	Leu	Xaa	Asn	Arg	Glu	Thr	Ser	Ile	Phe
				725					730					735	
Ser	Tyr	Arg	Glu	Asp	Pro	Ile	Val	Tyr	Glu	Ile	His	Pro	Thr	Lys	Ser
		740						745					750		
Phe	Ile	Ser	Gly	Gly	Ser	Thr	Ile	Thr	Gly	Val	Gly	Lys	Asn	Leu	Asn
	755						760					765			
Ser	Val	Ser	Val	Pro	Arg	Met	Val	Ile	Asn	Val	His	Glu	Ala	Gly	Arg
	770					775					780				
Asn	Phe	Thr	Val	Ala	Cys	Gln	His	Arg	Ser	Asn	Ser	Glu	Ile	Ile	Cys
785					790					795					800
Cys	Xaa	Thr	Pro	Ser	Leu	Gln	Gln	Leu	Asn	Leu	Gln	Leu	Pro	Leu	Lys
				805					810						815
Thr	Lys	Ala	Phe	Phe	Met	Leu	Asp	Gly	Ile	Leu	Ser	Lys	Tyr	Phe	Asp
			820					825					830		
Leu	Ile	Tyr	Val	His	Asn	Pro	Val	Phe	Lys	Pro	Phe	Glu	Lys	Pro	Val
	835						840					845			
Met	Ile	Ser	Met	Gly	Asn	Glu	Asn	Val	Leu	Glu	Ile	Lys	Gly	Asn	Asp
	850					855						860			
Ile	Asp	Pro	Glu	Ala	Val	Lys	Gly	Glu	Val	Leu	Lys	Val	Gly	Asn	Lys
865					870					875					880
Ser	Cys	Glu	Asn	Ile	His	Leu	His	Ser	Glu	Ala	Val	Leu	Cys	Thr	Val
				885					890					895	
Pro	Asn	Asp	Leu	Leu	Lys	Leu	Asn	Ser	Glu	Leu	Asn	Ile	Glu	Trp	Lys
			900					905					910		
Gln	Ala	Ile	Ser	Ser	Thr	Val	Leu	Gly	Lys	Val	Ile	Val	Gln	Pro	Asp
		915					920						925		
Gln	Asn	Phe	Thr	Gly	Leu	Ile	Ala	Gly	Val	Val	Ser	Ile	Ser	Thr	Ala
	930					935					940				
Leu	Leu	Leu	Leu	Leu	Gly	Phe	Phe	Leu	Trp	Leu	Lys	Lys	Arg	Lys	Gln
945					950					955					960
Ile	Lys	Asp	Leu	Gly	Ser	Glu	Leu	Val	Arg	Tyr	Asp	Ala	Arg	Val	His
				965					970					975	
Thr	Pro	His	Leu	Asp	Arg	Leu	Val	Ser	Ala	Arg	Ser	Val	Ser	Pro	Thr
			980					985					990		
Thr	Glu	Met	Val	Ser	Asn	Glu	Ser	Val	Asp	Tyr	Arg	Ala	Thr	Phe	Pro
		995						1000					1005		
Glu	Asp	Gln	Phe	Pro	Asn	Ser	Ser	Gln	Asn	Gly	Ser	Cys	Arg	Gln	Val
	1010					1015					1020				
Gln	Tyr	Pro	Leu	Thr	Asp	Met	Ser	Pro	Ile	Leu	Thr	Ser	Gly	Asp	Ser
1025					1030						1035				1040
Asp	Ile	Ser	Ser	Pro	Leu	Leu	Gln	Asn	Thr	Val	His	Ile	Asp	Leu	Ser
				1045					1050					1055	
Ala	Leu	Asn	Pro	Glu	Leu	Val	Gln	Ala	Val	Gln	His	Val	Val	Ile	Gly
			1060					1065						1070	
Pro	Ser	Ser	Leu	Ile	Val	His	Phe	Asn	Glu	Val	Ile	Gly	Arg	Gly	His
		1075						1080					1085		
Phe	Gly	Cys	Val	Tyr	Xaa	Gly	Thr	Leu	Leu	Asp	Xaa	Asp	Gly	Lys	Lys
	1090						1095					1100			

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Ile His Cys Ala Val Lys Ser Leu Asn Arg Ile Thr Asp Ile Gly Glu
1105          1110          1115          1120
Val Ser Gln Phe Leu Thr Glu Gly Ile Ile Met Lys Asp Phe Ser His
          1125          1130          1135
Pro Asn Val Leu Ser Leu Leu Gly Ile Cys Leu Arg Ser Glu Gly Ser
          1140          1145          1150
Pro Leu Val Val Leu Pro Tyr Met Lys His Gly Asp Leu Arg Asn Phe
          1155          1160          1165
Ile Arg Asn Glu Thr His Asn Pro Thr Val Lys Asp Leu Ile Gly Phe
          1170          1175          1180
Gly Leu Gln Val Ala Lys Gly Met Lys Tyr Leu Ala Ser Lys Lys Phe
1185          1190          1195          1200
Val His Arg Asp Leu Ala Ala Arg Asn Cys Met Leu Asp Glu Lys Phe
          1205          1210          1215
Thr Val Lys Val Ala Asp Phe Gly Leu Ala Arg Asp Met Xaa Asp Lys
          1220          1225          1230
Glu Tyr Xaa Ser Val His Asn Lys Thr Gly Ala Lys Leu Pro Val Lys
          1235          1240          1245
Trp Xaa Ala Leu Glu Ser Leu Gln Thr Gln Lys Phe Thr Thr Lys Ser
          1250          1255          1260
Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Leu Met Thr Arg Gly
1265          1270          1275          1280
Ala Pro Pro Tyr Pro Asp Val Asn Thr Phe Asp Ile Thr Val Tyr Leu
          1285          1290          1295
Leu Gln Gly Arg Arg Leu Leu Gln Pro Glu Tyr Cys Pro Asp Pro Leu
          1300          1305          1310
Tyr Glu Val Met Leu Lys Cys Trp His Pro Lys Ala Glu Met Arg Pro
          1315          1320          1325
Ser Phe Ser Glu Leu Val Ser Arg Ile Ser Ala Ile Phe Ser Thr Phe
          1330          1335          1340
Ile Gly Glu His Tyr Val His Val Asn Ala Thr Tyr Val Asn Val Lys
1345          1350          1355          1360
Cys Val Ala Pro Tyr Pro Ser Leu Leu Ser Ser Glu Asp Asn Ala Asp
          1365          1370          1375
Asp Glu Val Asp Thr Arg Pro Ala Ser Phe Trp Glu Thr Ser
          1380          1385          1390

```

```

<210> 307
<211> 1106
<212> PRT
<213> Homo sapiens

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```

<220>
<221> VARIANT
<222> 29
<223> Xaa = I or F

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```

<220>
<221> VARIANT
<222> 194
<223> Xaa = I or T

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<220>
<221> VARIANT
<222> 345

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&lt;223&gt; Xaa = P or S

&lt;400&gt; 307

```

Met Arg Leu Pro Gly Ala Met Pro Ala Leu Ala Leu Lys Gly Glu Leu
 1      5      10      15
Leu Leu Leu Ser Leu Leu Leu Leu Leu Glu Pro Gln Xaa Ser Gln Gly
 20      25      30
Leu Val Val Thr Pro Pro Gly Pro Glu Leu Val Leu Asn Val Ser Ser
 35      40      45
Thr Phe Val Leu Thr Cys Ser Gly Ser Ala Pro Val Val Trp Glu Arg
 50      55      60
Met Ser Gln Glu Pro Pro Gln Glu Met Ala Lys Ala Gln Asp Gly Thr
 65      70      75      80
Phe Ser Ser Val Leu Thr Leu Thr Asn Leu Thr Gly Leu Asp Thr Gly
 85      90      95
Glu Tyr Phe Cys Thr His Asn Asp Ser Arg Gly Leu Glu Thr Asp Glu
 100     105     110
Arg Lys Arg Leu Tyr Ile Phe Val Pro Asp Pro Thr Val Gly Phe Leu
 115     120     125
Pro Asn Asp Ala Glu Glu Leu Phe Ile Phe Leu Thr Glu Ile Thr Glu
 130     135     140
Ile Thr Ile Pro Cys Arg Val Thr Asp Pro Gln Leu Val Val Thr Leu
 145     150     155     160
His Glu Lys Lys Gly Asp Val Ala Leu Pro Val Pro Tyr Asp His Gln
 165     170     175
Arg Gly Phe Ser Gly Ile Phe Glu Asp Arg Ser Tyr Ile Cys Lys Thr
 180     185     190
Thr Xaa Gly Asp Arg Glu Val Asp Ser Asp Ala Tyr Tyr Val Tyr Arg
 195     200     205
Leu Gln Val Ser Ser Ile Asn Val Ser Val Asn Ala Val Gln Thr Val
 210     215     220
Val Arg Gln Gly Glu Asn Ile Thr Leu Met Cys Ile Val Ile Gly Asn
 225     230     235     240
Glu Val Val Asn Phe Glu Trp Thr Tyr Pro Arg Lys Glu Ser Gly Arg
 245     250     255
Leu Val Glu Pro Val Thr Asp Phe Leu Leu Asp Met Pro Tyr His Ile
 260     265     270
Arg Ser Ile Leu His Ile Pro Ser Ala Glu Leu Glu Asp Ser Gly Thr
 275     280     285
Tyr Thr Cys Asn Val Thr Glu Ser Val Asn Asp His Gln Asp Glu Lys
 290     295     300
Ala Ile Asn Ile Thr Val Val Glu Ser Gly Tyr Val Arg Leu Leu Gly
 305     310     315     320
Glu Val Gly Thr Leu Gln Phe Ala Glu Leu His Arg Ser Arg Thr Leu
 325     330     335
Gln Val Val Phe Glu Ala Tyr Pro Xaa Pro Thr Val Leu Trp Phe Lys
 340     345     350
Asp Asn Arg Thr Leu Gly Asp Ser Ser Ala Gly Glu Ile Ala Leu Ser
 355     360     365
Thr Arg Asn Val Ser Glu Thr Arg Tyr Val Ser Glu Leu Thr Leu Val
 370     375     380
Arg Val Lys Val Ala Glu Ala Gly His Tyr Thr Met Arg Ala Phe His
 385     390     395     400
Glu Asp Ala Glu Val Gln Leu Ser Phe Gln Leu Gln Ile Asn Val Pro
 405     410     415
Val Arg Val Leu Glu Leu Ser Glu Ser His Pro Asp Ser Gly Glu Gln

```

			420						425						430			
Thr	Val	Arg	Cys	Arg	Gly	Arg	Gly	Met	Pro	Gln	Pro	Asn	Ile	Ile	Trp			
		435					440					445						
Ser	Ala	Cys	Arg	Asp	Leu	Lys	Arg	Cys	Pro	Arg	Glu	Leu	Pro	Pro	Thr			
	450					455					460							
Leu	Leu	Gly	Asn	Ser	Ser	Glu	Glu	Glu	Ser	Gln	Leu	Glu	Thr	Asn	Val			
465					470					475					480			
Thr	Tyr	Trp	Glu	Glu	Glu	Gln	Glu	Phe	Glu	Val	Val	Ser	Thr	Leu	Arg			
			485						490					495				
Leu	Gln	His	Val	Asp	Arg	Pro	Leu	Ser	Val	Arg	Cys	Thr	Leu	Arg	Asn			
			500					505					510					
Ala	Val	Gly	Gln	Asp	Thr	Gln	Glu	Val	Ile	Val	Val	Pro	His	Ser	Leu			
	515						520					525						
Pro	Phe	Lys	Val	Val	Val	Ile	Ser	Ala	Ile	Leu	Ala	Leu	Val	Val	Leu			
	530					535				540								
Thr	Ile	Ile	Ser	Leu	Ile	Ile	Leu	Ile	Met	Leu	Trp	Gln	Lys	Lys	Pro			
545				550					555						560			
Arg	Tyr	Glu	Ile	Arg	Trp	Lys	Val	Ile	Glu	Ser	Val	Ser	Ser	Asp	Gly			
			565						570					575				
His	Glu	Tyr	Ile	Tyr	Val	Asp	Pro	Met	Gln	Leu	Pro	Tyr	Asp	Ser	Thr			
			580					585					590					
Trp	Glu	Leu	Pro	Arg	Asp	Gln	Leu	Val	Leu	Gly	Arg	Thr	Leu	Gly	Ser			
		595					600					605						
Gly	Ala	Phe	Gly	Gln	Val	Val	Glu	Ala	Thr	Ala	His	Gly	Leu	Ser	His			
	610					615					620							
Ser	Gln	Ala	Thr	Met	Lys	Val	Ala	Val	Lys	Met	Leu	Lys	Ser	Thr	Ala			
625					630					635					640			
Arg	Ser	Ser	Glu	Lys	Gln	Ala	Leu	Met	Ser	Glu	Leu	Lys	Ile	Met	Ser			
			645						650					655				
His	Leu	Gly	Pro	His	Leu	Asn	Val	Val	Asn	Leu	Leu	Gly	Ala	Cys	Thr			
			660					665					670					
Lys	Gly	Gly	Pro	Ile	Tyr	Ile	Ile	Thr	Glu	Tyr	Cys	Arg	Tyr	Gly	Asp			
		675					680					685						
Leu	Val	Asp	Tyr	Leu	His	Arg	Asn	Lys	His	Thr	Phe	Leu	Gln	His	His			
	690					695					700							
Ser	Asp	Lys	Arg	Arg	Pro	Ser	Ala	Glu	Leu	Tyr	Ser	Asn	Ala	Leu				
705					710				715					720				
Pro	Val	Gly	Leu	Pro	Leu	Pro	Ser	His	Val	Ser	Leu	Thr	Gly	Glu	Ser			
			725						730					735				
Asp	Gly	Gly	Tyr	Met	Asp	Met	Ser	Lys	Asp	Glu	Ser	Val	Asp	Tyr	Val			
			740					745					750					
Pro	Met	Leu	Asp	Met	Lys	Gly	Asp	Val	Lys	Tyr	Ala	Asp	Ile	Glu	Ser			
		755					760					765	</					

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865      870      875      880
Thr Thr Leu Ser Asp Val Trp Ser Phe Gly Ile Leu Leu Trp Glu Ile
      885      890      895
Phe Thr Leu Gly Thr Pro Tyr Pro Glu Leu Pro Met Asn Glu Gln
      900      905      910
Phe Tyr Asn Ala Ile Lys Arg Gly Tyr Arg Met Ala Gln Pro Ala His
      915      920      925
Ala Ser Asp Glu Ile Tyr Glu Ile Met Gln Lys Cys Trp Glu Glu Lys
      930      935      940
Phe Glu Ile Arg Pro Pro Phe Ser Gln Leu Val Leu Leu Leu Glu Arg
945      950      955      960
Leu Leu Gly Glu Gly Tyr Lys Lys Lys Tyr Gln Gln Val Asp Glu Glu
      965      970      975
Phe Leu Arg Ser Asp His Pro Ala Ile Leu Arg Ser Gln Ala Arg Leu
      980      985      990
Pro Gly Phe His Gly Leu Arg Ser Pro Leu Asp Thr Ser Ser Val Leu
      995      1000      1005
Tyr Thr Ala Val Gln Pro Asn Glu Gly Asp Asn Asp Tyr Ile Ile Pro
1010      1015      1020
Leu Pro Asp Pro Lys Pro Glu Val Ala Asp Glu Gly Pro Leu Glu Gly
1025      1030      1035      1040
Ser Pro Ser Leu Ala Ser Ser Thr Leu Asn Glu Val Asn Thr Ser Ser
      1045      1050      1055
Thr Ile Ser Cys Asp Ser Pro Leu Glu Pro Gln Asp Glu Pro Glu Pro
      1060      1065      1070
Glu Pro Gln Leu Glu Leu Gln Val Glu Pro Glu Pro Glu Leu Glu Gln
      1075      1080      1085
Leu Pro Asp Ser Gly Cys Pro Ala Pro Arg Ala Glu Ala Glu Asp Ser
1090      1095      1100
Phe Leu
1105

```

```

<210> 308
<211> 1400
<212> PRT
<213> Homo sapiens

```

```

<220>
<221> VARIANT
<222> 113, 1195
<223> Xaa = G or S

```

```

<220>
<221> VARIANT
<222> 209
<223> Xaa = G or A

```

```

<220>
<221> VARIANT
<222> 322, 523
<223> Xaa = Q or R

```

```

<220>
<221> VARIANT
<222> 440

```

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&lt;223&gt; Xaa = N or S

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 946

&lt;223&gt; Xaa = V or M

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 1232

&lt;223&gt; Xaa = R or G or D or V

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 1254

&lt;223&gt; Xaa = M or T

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 1335

&lt;223&gt; Xaa = R or G

&lt;400&gt; 308

Met	Glu	Leu	Leu	Pro	Pro	Leu	Pro	Gln	Ser	Phe	Leu	Leu	Leu	Leu	Leu
1				5					10					15	
Leu	Pro	Ala	Lys	Pro	Ala	Ala	Gly	Glu	Asp	Trp	Gln	Cys	Pro	Arg	Thr
			20					25					30		
Pro	Tyr	Ala	Ala	Ser	Arg	Asp	Phe	Asp	Val	Lys	Tyr	Val	Val	Pro	Ser
		35					40					45			
Phe	Ser	Ala	Gly	Gly	Leu	Val	Gln	Ala	Met	Val	Thr	Tyr	Glu	Gly	Asp
	50					55					60				
Arg	Asn	Glu	Ser	Ala	Val	Phe	Val	Ala	Ile	Arg	Asn	Arg	Leu	His	Val
65					70					75				80	
Leu	Gly	Pro	Asp	Leu	Lys	Ser	Val	Gln	Ser	Leu	Ala	Thr	Gly	Pro	Ala
				85					90					95	
Gly	Asp	Pro	Gly	Cys	Gln	Thr	Cys	Ala	Ala	Cys	Gly	Pro	Gly	Pro	His
			100					105					110		
Xaa	Pro	Pro	Gly	Asp	Thr	Asp	Thr	Lys	Val	Leu	Val	Leu	Asp	Pro	Ala
		115					120					125			
Leu	Pro	Ala	Leu	Val	Ser	Cys	Gly	Ser	Ser	Leu	Gln	Gly	Arg	Cys	Phe
	130					135					140				
Leu	His	Asp	Leu	Glu	Pro	Gln	Gly	Thr	Ala	Val	His	Leu	Ala	Ala	Pro
145					150					155					160
Ala	Cys	Leu	Phe	Ser	Ala	His	His	Asn	Arg	Pro	Asp	Asp	Cys	Pro	Asp
			165						170					175	
Cys	Val	Ala	Ser	Pro	Leu	Gly	Thr	Arg	Val	Thr	Val	Val	Glu	Gln	Gly
			180					185					190		
Gln	Ala	Ser	Tyr	Phe	Tyr	Val	Ala	Ser	Ser	Leu	Asp	Ala	Ala	Val	Ala
		195					200					205			
Xaa	Ser	Phe	Ser	Pro	Arg	Ser	Val	Ser	Ile	Arg	Arg	Leu	Lys	Ala	Asp
	210					215					220				
Ala	Ser	Gly	Phe	Ala	Pro	Gly	Phe	Val	Ala	Leu	Ser	Val	Leu	Pro	Lys
225					230					235					240
His	Leu	Val	Ser	Tyr	Ser	Ile	Glu	Tyr	Val	His	Ser	Phe	His	Thr	Gly
				245					250					255	
Ala	Phe	Val	Tyr	Phe	Leu	Thr	Val	Gln	Pro	Ala	Ser	Val	Thr	Asp	Asp

				260										270					
Pro	Ser	Ala	Leu	His	Thr	Arg	Leu	Ala	Arg	Leu	Ser	Ala	Thr	Glu	Pro				
		275					280					285							
Glu	Leu	Gly	Asp	Tyr	Arg	Glu	Leu	Val	Leu	Asp	Cys	Arg	Phe	Ala	Pro				
	290					295					300								
Lys	Arg	Arg	Arg	Arg	Gly	Ala	Pro	Glu	Gly	Gly	Gln	Pro	Tyr	Pro	Val				
305					310					315					320				
Leu	Xaa	Val	Ala	His	Ser	Ala	Pro	Val	Gly	Ala	Gln	Leu	Ala	Thr	Glu				
				325					330						335				
Leu	Ser	Ile	Ala	Glu	Gly	Gln	Glu	Val	Leu	Phe	Gly	Val	Phe	Val	Thr				
			340					345					350						
Gly	Lys	Asp	Gly	Gly	Pro	Gly	Val	Gly	Pro	Asn	Ser	Val	Val	Cys	Ala				
		355					360					365							
Phe	Pro	Ile	Asp	Leu	Leu	Asp	Thr	Leu	Ile	Asp	Glu	Gly	Val	Glu	Arg				
	370					375					380								
Cys	Cys	Glu	Ser	Pro	Val	His	Pro	Gly	Leu	Arg	Arg	Gly	Leu	Asp	Phe				
385					390					395					400				
Phe	Gln	Ser	Pro	Ser	Phe	Cys	Pro	Asn	Pro	Pro	Gly	Leu	Glu	Ala	Leu				
				405					410					415					
Ser	Pro	Asn	Thr	Ser	Cys	Arg	His	Phe	Pro	Leu	Leu	Val	Ser	Ser	Ser				
			420					425					430						
Phe	Ser	Arg	Val	Asp	Leu	Phe	Xaa	Gly	Leu	Leu	Gly	Pro	Val	Gln	Val				
		435					440					445							
Thr	Ala	Leu	Tyr	Val	Thr	Arg	Leu	Asp	Asn	Val	Thr	Val	Ala	His	Met				
	450					455					460								
Gly	Thr	Met	Asp	Gly	Arg	Ile	Leu	Gln	Val	Glu	Leu	Val	Arg	Ser	Leu				
465					470					475					480				
Asn	Tyr	Leu	Leu	Tyr	Val	Ser	Asn	Phe	Ser	Leu	Gly	Asp	Ser	Gly	Gln				
				485					490					495					
Pro	Val	Gln	Arg	Asp	Val	Ser	Arg	Leu	Gly	Asp	His	Leu	Leu	Phe	Ala				
			500					505				510							
Ser	Gly	Asp	Gln	Val	Phe	Gln	Val	Pro	Ile	Xaa	Gly	Pro	Gly	Cys	Arg				
		515					520					525							
His	Phe	Leu	Thr	Cys	Gly	Arg	Cys	Leu	Arg	Ala	Trp	His	Phe	Met	Gly				
	530				535						540								
Cys	Gly	Trp	Cys	Gly	Asn	Met	Cys	Gly	Gln	Gln	Lys	Glu	Cys	Pro	Gly				
545					550					555					560				
Ser	Trp	Gln	Gln	Asp	His	Cys	Pro	Pro	Lys	Leu	Thr	Glu	Phe	His	Pro				
				565					570					575					
His	Ser	Gly	Pro	Leu	Arg	Gly	Ser	Thr	Arg	Leu	Thr	Leu	Cys	Gly	Ser				
			580					585					590						
Asn	Phe	Tyr	Leu	His	Pro	Ser	Gly	Leu	Val	Pro	Glu	Gly	Thr	His	Gln				
		595					600					605							

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705					710					715				720
Gly	Thr	Glu	Cys	Leu	Leu	Ala	Arg	Val	Ser	Glu	Gly	Gln	Leu	Leu
				725						730				735
Ala	Thr	Pro	Pro	Gly	Ala	Thr	Val	Ala	Ser	Val	Pro	Leu	Ser	Leu
				740						745				750
Val	Gly	Gly	Ala	Gln	Val	Pro	Gly	Ser	Trp	Thr	Phe	Gln	Tyr	Arg
				755						760				765
Asp	Pro	Val	Val	Leu	Ser	Ile	Ser	Pro	Asn	Cys	Gly	Tyr	Ile	Asn
				770						780				
His	Ile	Thr	Ile	Cys	Gly	Gln	His	Leu	Thr	Ser	Ala	Trp	His	Leu
				785						795				800
Leu	Ser	Phe	His	Asp	Gly	Leu	Arg	Ala	Val	Glu	Ser	Arg	Cys	Glu
				805						810				815
Gln	Leu	Pro	Glu	Gln	Gln	Leu	Cys	Arg	Leu	Pro	Glu	Tyr	Val	Val
				820						825				830
Asp	Pro	Gln	Gly	Trp	Val	Ala	Gly	Asn	Leu	Ser	Ala	Arg	Gly	Asp
				835						840				845
Ala	Ala	Gly	Phe	Thr	Leu	Pro	Gly	Phe	Arg	Phe	Leu	Pro	Pro	Pro
				850						855				860
Pro	Pro	Ser	Ala	Asn	Leu	Val	Pro	Leu	Lys	Pro	Glu	Glu	His	Ala
				865						870				875
Lys	Phe	Glu	Tyr	Ile	Gly	Leu	Gly	Ala	Val	Ala	Asp	Cys	Val	Gly
				885						890				895
Asn	Val	Thr	Val	Gly	Gly	Glu	Ser	Cys	Gln	His	Glu	Phe	Arg	Gly
				900						905				910
Met	Val	Val	Cys	Pro	Leu	Pro	Pro	Ser	Leu	Gln	Leu	Gly	Gln	Asp
				915						920				925
Ala	Pro	Leu	Gln	Val	Cys	Val	Asp	Gly	Glu	Cys	His	Ile	Leu	Gly
				930						935				940
Val	Xaa	Arg	Pro	Gly	Pro	Asp	Gly	Val	Pro	Gln	Ser	Thr	Leu	Leu
				945						950				955
Ile	Leu	Leu	Pro	Leu	Leu	Leu	Leu	Val	Ala	Ala	Leu	Ala	Thr	Ala
				965						970				975
Val	Phe	Ser	Tyr	Trp	Trp	Arg	Arg	Lys	Gln	Leu	Val	Leu	Pro	Pro
				980						985				990
Leu	Asn	Asp	Leu	Ala	Ser	Leu	Asp	Gln	Thr	Ala	Gly	Ala	Thr	Pro
				995						1000				1005
Pro	Ile	Leu	Tyr	Ser	Gly	Ser	Asp	Tyr	Arg	Ser	Gly	Leu	Ala	Leu
				1010						1015				1020
Ala	Ile	Asp	Gly	Leu	Asp	Ser	Thr	Thr	Cys	Val	His	Gly	Ala	Ser
				1025						1030				1035
Ser	Asp	Ser	Glu	Asp	Glu	Ser	Cys	Val	Pro	Leu	Leu	Arg	Lys	Glu
				1045						1050				1055
Ile	Gln	Leu	Arg	Asp	Leu	Asp	Ser	Ala	Leu	Leu	Ala	Glu	Val	Lys
				1060						1065				1070
Val	Leu	Ile	Pro	His	Glu	Arg	Val	Val	Thr	His	Ser	Asp	Arg	Val
				1075						1080				1085
Gly	Lys	Gly	His	Phe	Gly	Val	Val	Tyr	His	Gly	Glu	Tyr	Ile	Asp
				1090						1095				1100
Ala	Gln	Asn	Arg	Ile	Gln	Cys	Ala	Ile	Lys	Ser	Leu	Ser	Arg	Ile
				1105						1110				1115
Glu	Met	Gln	Gln	Val	Glu	Ala	Phe	Leu	Arg	Glu	Gly	Leu	Leu	Met
				1125						1130				1135
Gly	Leu	Asn	His	Pro	Asn	Val	Leu	Ala	Leu	Ile	Gly	Ile	Met	Leu
				1140						1145				1150
Pro	Glu	Gly	Leu	Pro	His	Val	Leu	Leu	Pro	Tyr	Met	Cys	His	Gly



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      1155      1160      1165
Leu Leu Gln Phe Ile Arg Ser Pro Gln Arg Asn Pro Thr Val Lys Asp
      1170      1175      1180
Leu Ile Ser Phe Gly Leu Gln Val Ala Arg Xaa Met Glu Tyr Leu Ala
1185      1190      1195      1200
Glu Gln Lys Phe Val His Arg Asp Leu Ala Ala Arg Asn Cys Met Leu
      1205      1210      1215
Asp Glu Ser Phe Thr Val Lys Val Ala Asp Phe Gly Leu Ala Arg Xaa
      1220      1225      1230
Ile Leu Asp Arg Glu Tyr Tyr Ser Val Gln Gln His Arg His Ala Arg
      1235      1240      1245
Leu Pro Val Lys Trp Xaa Ala Leu Glu Ser Leu Gln Thr Tyr Arg Phe
      1250      1255      1260
Thr Thr Lys Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Leu
1265      1270      1275      1280
Leu Thr Arg Gly Ala Pro Pro Tyr Arg His Ile Asp Pro Phe Asp Leu
      1285      1290      1295
Thr His Phe Leu Ala Gln Gly Arg Arg Leu Pro Gln Pro Glu Tyr Cys
      1300      1305      1310
Pro Asp Ser Leu Tyr Gln Val Met Gln Gln Cys Trp Glu Ala Asp Pro
      1315      1320      1325
Ala Val Arg Pro Thr Phe Xaa Val Leu Val Gly Glu Val Glu Gln Ile
      1330      1335      1340
Val Ser Ala Leu Leu Gly Asp His Tyr Val Gln Leu Pro Ala Thr Tyr
1345      1350      1355      1360
Met Asn Leu Gly Pro Ser Thr Ser His Glu Met Asn Val Arg Pro Glu
      1365      1370      1375
Gln Pro Gln Phe Ser Pro Met Pro Gly Asn Val Arg Arg Pro Arg Pro
      1380      1385      1390
Leu Ser Glu Pro Pro Arg Pro Thr
      1395      1400

```

```

<210> 309
<211> 1124
<212> PRT
<213> Homo sapiens

```

```

<220>
<221> VARIANT
<222> 346
<223> Xaa = P or Q

```

```

<220>
<221> VARIANT
<222> 486
<223> Xaa = V or I

```

```

<220>
<221> VARIANT
<222> 695
<223> Xaa = I or T

```

```

<220>
<221> VARIANT
<222> 724

```

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&lt;223&gt; Xaa = A or T

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 849

&lt;223&gt; Xaa = R or W

&lt;400&gt; 309

```

Met Asp Ser Leu Ala Ser Leu Val Leu Cys Gly Val Ser Leu Leu Leu
 1          5          10          15
Ser Gly Thr Val Glu Gly Ala Met Asp Leu Ile Leu Ile Asn Ser Leu
 20          25          30
Pro Leu Val Ser Asp Ala Glu Thr Ser Leu Thr Cys Ile Ala Ser Gly
 35          40          45
Trp Arg Pro His Glu Pro Ile Thr Ile Gly Arg Asp Phe Glu Ala Leu
 50          55          60
Met Asn Gln His Gln Asp Pro Leu Glu Val Thr Gln Asp Val Thr Arg
 65          70          75          80
Glu Trp Ala Lys Lys Val Val Trp Lys Arg Glu Lys Ala Ser Lys Ile
 85          90          95
Asn Gly Ala Tyr Phe Cys Glu Gly Arg Val Arg Gly Glu Ala Ile Arg
100          105          110
Ile Arg Thr Met Lys Met Arg Gln Gln Ala Ser Phe Leu Pro Ala Thr
115          120          125
Leu Thr Met Thr Val Asp Lys Gly Asp Asn Val Asn Ile Ser Phe Lys
130          135          140
Lys Val Leu Ile Lys Glu Glu Asp Ala Val Ile Tyr Lys Asn Gly Ser
145          150          155          160
Phe Ile His Ser Val Pro Arg His Glu Val Pro Asp Ile Leu Glu Val
165          170          175
His Leu Pro His Ala Gln Pro Gln Asp Ala Gly Val Tyr Ser Ala Arg
180          185          190
Tyr Ile Gly Gly Asn Leu Phe Thr Ser Ala Phe Thr Arg Leu Ile Val
195          200          205
Arg Arg Cys Glu Ala Gln Lys Trp Gly Pro Glu Cys Asn His Leu Cys
210          215          220
Thr Ala Cys Met Asn Asn Gly Val Cys His Glu Asp Thr Gly Glu Cys
225          230          235          240
Ile Cys Pro Pro Gly Phe Met Gly Arg Thr Cys Glu Lys Ala Cys Glu
245          250          255
Leu His Thr Phe Gly Arg Thr Cys Lys Glu Arg Cys Ser Gly Gln Glu
260          265          270
Gly Cys Lys Ser Tyr Val Phe Cys Leu Pro Asp Pro Tyr Gly Cys Ser
275          280          285
Cys Ala Thr Gly Trp Lys Gly Leu Gln Cys Asn Glu Ala Cys His Pro
290          295          300
Gly Phe Tyr Gly Pro Asp Cys Lys Leu Arg Cys Ser Cys Asn Asn Gly
305          310          315          320
Glu Met Cys Asp Arg Phe Gln Gly Cys Leu Cys Ser Pro Gly Trp Gln
325          330          335
Gly Leu Gln Cys Glu Arg Glu Gly Ile Xaa Arg Met Thr Pro Lys Ile
340          345          350
Val Asp Leu Pro Asp His Ile Glu Val Asn Ser Gly Lys Phe Asn Pro
355          360          365
Ile Cys Lys Ala Ser Gly Trp Pro Leu Pro Thr Asn Glu Glu Met Thr
370          375          380

```

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Leu	Val	Lys	Pro	Asp	Gly	Thr	Val	Leu	His	Pro	Lys	Asp	Phe	Asn	His	385	390	395	400
Thr	Asp	His	Phe	Ser	Val	Ala	Ile	Phe	Thr	Ile	His	Arg	Ile	Leu	Pro		405	410	415
Pro	Asp	Ser	Gly	Val	Trp	Val	Cys	Ser	Val	Asn	Thr	Val	Ala	Gly	Met		420	425	430
Val	Glu	Lys	Pro	Phe	Asn	Ile	Ser	Val	Lys	Val	Leu	Pro	Lys	Pro	Leu		435	440	445
Asn	Ala	Pro	Asn	Val	Ile	Asp	Thr	Gly	His	Asn	Phe	Ala	Val	Ile	Asn		450	455	460
Ile	Ser	Ser	Glu	Pro	Tyr	Phe	Gly	Asp	Gly	Pro	Ile	Lys	Ser	Lys	Lys		465	470	475
Leu	Leu	Tyr	Lys	Pro	Xaa	Asn	His	Tyr	Glu	Ala	Trp	Gln	His	Ile	Gln		485	490	495
Val	Thr	Asn	Glu	Ile	Val	Thr	Leu	Asn	Tyr	Leu	Glu	Pro	Arg	Thr	Glu		500	505	510
Tyr	Glu	Leu	Cys	Val	Gln	Leu	Val	Arg	Arg	Gly	Glu	Gly	Gly	Glu	Gly		515	520	525
His	Pro	Gly	Pro	Val	Arg	Arg	Phe	Thr	Thr	Ala	Ser	Ile	Gly	Leu	Pro		530	535	540
Pro	Pro	Arg	Gly	Leu	Asn	Leu	Leu	Pro	Lys	Ser	Gln	Thr	Thr	Leu	Asn		545	550	555
Leu	Thr	Trp	Gln	Pro	Ile	Phe	Pro	Ser	Ser	Glu	Asp	Asp	Phe	Tyr	Val		565	570	575
Glu	Val	Glu	Arg	Ser	Val	Gln	Lys	Ser	Asp	Gln	Gln	Asn	Ile	Lys			580	585	590
Val	Pro	Gly	Asn	Leu	Thr	Ser	Val	Leu	Leu	Asn	Asn	Leu	His	Pro	Arg		595	600	605
Glu	Gln	Tyr	Val	Val	Arg	Ala	Arg	Val	Asn	Thr	Lys	Ala	Gln	Gly	Glu		610	615	620
Trp	Ser	Glu	Asp	Leu	Thr	Ala	Trp	Thr	Leu	Ser	Asp	Ile	Leu	Pro	Pro		625	630	635
Gln	Pro	Glu	Asn	Ile	Lys	Ile	Ser	Asn	Ile	Thr	His	Ser	Ser	Ala	Val		645	650	655
Ile	Ser	Trp	Thr	Ile	Leu	Asp	Gly	Tyr	Ser	Ile	Ser	Ser	Ile	Thr	Ile		660	665	670
Arg	Tyr	Lys	Val	Gln	Gly	Lys	Asn	Glu	Asp	Gln	His	Val	Asp	Val	Lys		675	680	685
Ile	Lys	Asn	Ala	Thr	Ile	Xaa	Gln	Tyr	Gln	Leu	Lys	Gly	Leu	Glu	Pro		690	695	700
Glu	Thr	Ala	Tyr	Gln	Val	Asp	Ile	Phe	Ala	Glu	Asn	Asn	Ile	Gly	Ser		705	710	715
Ser	Asn	Pro	Xaa	Phe	Ser	His	Glu	Leu	Val	Thr	Leu	Pro	Glu	Ser	Gln		725	730	735
Ala	Pro	Ala	Asp	Leu	Gly	Gly	Gly	Lys	Met	Leu	Leu	Ile	Ala	Ile	Leu		740	745	750
Gly	Ser	Ala	Gly	Met	Thr	Cys	Leu	Thr	Val	Leu	Leu	Ala	Phe	Leu	Ile		755	760	765
Ile	Leu	Gln	Leu	Lys	Arg	Ala	Asn	Val	Gln	Arg	Arg	Met	Ala	Gln	Ala		770	775	780
Phe	Gln	Asn	Val	Arg	Glu	Glu	Pro	Ala	Val	Gln	Phe	Asn	Ser	Gly	Thr		785	790	795
Leu	Ala	Leu	Asn	Arg	Lys	Val	Lys	Asn	Asn	Pro	Asp	Pro	Thr	Ile	Tyr		805	810	815
Pro	Val	Leu	Asp	Trp	Asn	Asp	Ile	Lys	Phe	Gln	Asp	Val	Ile	Gly	Glu		820	825	830

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Gly Asn Phe Gly Gln Val Leu Lys Ala Arg Ile Lys Lys Asp Gly Leu  
           835                  840          845  
 Xaa Met Asp Ala Ala Ile Lys Arg Met Lys Glu Tyr Ala Ser Lys Asp  
           850                  855          860  
 Asp His Arg Asp Phe Ala Gly Glu Leu Glu Val Leu Cys Lys Leu Gly  
  865                  870          875          880  
 His His Pro Asn Ile Ile Asn Leu Leu Gly Ala Cys Glu His Arg Gly  
           885                  890          895  
 Tyr Leu Tyr Leu Ala Ile Glu Tyr Ala Pro His Gly Asn Leu Leu Asp  
           900                  905          910  
 Phe Leu Arg Lys Ser Arg Val Leu Glu Thr Asp Pro Ala Phe Ala Ile  
           915                  920          925  
 Ala Asn Ser Thr Ala Ser Thr Leu Ser Ser Gln Gln Leu Leu His Phe  
           930                  935          940  
 Ala Ala Asp Val Ala Arg Gly Met Asp Tyr Leu Ser Gln Lys Gln Phe  
  945                  950          955          960  
 Ile His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Gly Glu Asn Tyr  
           965                  970          975  
 Val Ala Lys Ile Ala Asp Phe Gly Leu Ser Arg Gly Gln Glu Val Tyr  
           980                  985          990  
 Val Lys Lys Thr Met Gly Arg Leu Pro Val Arg Trp Met Ala Ile Glu  
           995                 1000         1005  
 Ser Leu Asn Tyr Ser Val Tyr Thr Thr Asn Ser Asp Val Trp Ser Tyr  
  1010                 1015         1020  
 Gly Val Leu Leu Trp Glu Ile Val Ser Leu Gly Gly Thr Pro Tyr Cys  
  1025                 1030         1035         1040  
 Gly Met Thr Cys Ala Glu Leu Tyr Glu Lys Leu Pro Gln Gly Tyr Arg  
           1045                 1050         1055  
 Leu Glu Lys Pro Leu Asn Cys Asp Asp Glu Val Tyr Asp Leu Met Arg  
           1060                 1065         1070  
 Gln Cys Trp Arg Glu Lys Pro Tyr Glu Arg Pro Ser Phe Ala Gln Ile  
           1075                 1080         1085  
 Leu Val Ser Leu Asn Arg Met Leu Glu Glu Arg Lys Thr Tyr Val Asn  
  1090                 1095         1100  
 Thr Thr Leu Tyr Glu Lys Phe Thr Tyr Ala Gly Ile Asp Cys Ser Ala  
  1105                 1110         1115         1120  
 Glu Glu Ala Ala

<210> 310  
 <211> 1138  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 142  
 <223> Xaa = A or T

<220>  
 <221> VARIANT  
 <222> 1109  
 <223> Xaa = R or C

<400> 310

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Met	Val	Trp	Arg	Val	Pro	Pro	Phe	Leu	Leu	Pro	Ile	Leu	Phe	Leu	Ala
1				5				10						15	
Ser	His	Val	Gly	Ala	Ala	Val	Asp	Leu	Thr	Leu	Leu	Ala	Asn	Leu	Arg
			20					25					30		
Leu	Thr	Asp	Pro	Gln	Arg	Phe	Phe	Leu	Thr	Cys	Val	Ser	Gly	Glu	Ala
		35				40						45			
Gly	Ala	Gly	Arg	Gly	Ser	Asp	Ala	Trp	Gly	Pro	Pro	Leu	Leu	Leu	Glu
	50					55				60					
Lys	Asp	Asp	Arg	Ile	Val	Arg	Thr	Pro	Pro	Gly	Pro	Pro	Leu	Arg	Leu
65				70						75				80	
Ala	Arg	Asn	Gly	Ser	His	Gln	Val	Thr	Leu	Arg	Gly	Phe	Ser	Lys	Pro
			85						90					95	
Ser	Asp	Leu	Val	Gly	Val	Phe	Ser	Cys	Val	Gly	Gly	Ala	Gly	Ala	Arg
		100						105					110		
Arg	Thr	Arg	Val	Ile	Tyr	Val	His	Asn	Ser	Pro	Gly	Ala	His	Leu	Leu
	115						120					125			
Pro	Asp	Lys	Val	Thr	His	Thr	Val	Asn	Lys	Gly	Asp	Thr	Xaa	Val	Leu
	130					135					140				
Ser	Ala	Arg	Val	His	Lys	Glu	Lys	Gln	Thr	Asp	Val	Ile	Trp	Lys	Ser
145				150						155				160	
Asn	Gly	Ser	Tyr	Phe	Tyr	Thr	Leu	Asp	Trp	His	Glu	Ala	Gln	Asp	Gly
			165					170						175	
Arg	Phe	Leu	Leu	Gln	Leu	Pro	Asn	Val	Gln	Pro	Pro	Ser	Ser	Gly	Ile
		180						185					190		
Tyr	Ser	Ala	Thr	Tyr	Leu	Glu	Ala	Ser	Pro	Leu	Gly	Ser	Ala	Phe	Phe
	195						200					205			
Arg	Leu	Ile	Val	Arg	Gly	Cys	Gly	Ala	Gly	Arg	Trp	Gly	Pro	Gly	Cys
	210				215					220					
Thr	Lys	Glu	Cys	Pro	Gly	Cys	Leu	His	Gly	Gly	Val	Cys	His	Asp	His
225				230						235				240	
Asp	Gly	Glu	Cys	Val	Cys	Pro	Pro	Gly	Phe	Thr	Gly	Thr	Arg	Cys	Glu
			245						250					255	
Gln	Ala	Cys	Arg	Glu	Gly	Arg	Phe	Gly	Gln	Ser	Cys	Gln	Glu	Gln	Cys
		260						265					270		
Pro	Gly	Ile	Ser	Gly	Cys	Arg	Gly	Leu	Thr	Phe	Cys	Leu	Pro	Asp	Pro
	275						280					285			
Tyr	Gly	Cys	Ser	Cys	Gly	Ser	Gly	Trp	Arg	Gly	Ser	Gln	Cys	Gln	Glu
	290					295				300					
Ala	Cys	Ala	Pro	Gly	His	Phe	Gly	Ala	Asp	Cys	Arg	Leu	Gln	Cys	Gln
305				310						315				320	
Cys	Gln	Asn	Gly	Gly	Thr	Cys	Asp	Arg	Phe	Ser	Gly	Cys	Val	Cys	Pro
			325						330					335	
Ser	Gly	Trp	His	Gly	Val	His	Cys	Glu	Lys	Ser	Asp	Arg	Ile	Pro	Gln
		340						345					350		
Ile	Leu	Asn	Met	Ala	Ser	Glu	Leu	Glu	Phe	Asn	Leu	Glu	Thr	Met	Pro
	355					360						365			
Arg	Ile	Asn	Cys	Ala	Ala	Ala	Gly	Asn	Pro	Phe	Pro	Val	Arg	Gly	Ser
	370					375					380				
Ile	Glu	Leu	Arg	Lys	Pro	Asp	Gly	Thr	Val	Leu	Leu	Ser	Thr	Lys	Ala
385				390						395				400	
Ile	Val	Glu	Pro	Glu	Lys	Thr	Thr	Ala	Glu	Phe	Glu	Val	Pro	Arg	Leu
			405						410					415	
Val	Leu	Ala	Asp	Ser	Gly	Phe	Trp	Glu	Cys	Arg	Val	Ser	Thr	Ser	Gly
		420						425					430		
Gly	Gln	Asp	Ser	Arg	Arg	Phe	Lys	Val	Asn	Val	Lys	Val	Pro	Pro	Val
		435					440					445			

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Pro	Leu	Ala	Ala	Pro	Arg	Leu	Leu	Thr	Lys	Gln	Ser	Arg	Gln	Leu	Val
450						455					460				
Val	Ser	Pro	Leu	Val	Ser	Phe	Ser	Gly	Asp	Gly	Pro	Ile	Ser	Thr	Val
465					470					475					480
Arg	Leu	His	Tyr	Arg	Pro	Gln	Asp	Ser	Thr	Met	Asp	Trp	Ser	Thr	Ile
				485					490						495
Val	Val	Asp	Pro	Ser	Glu	Asn	Val	Thr	Leu	Met	Asn	Leu	Arg	Pro	Lys
			500					505					510		
Thr	Gly	Tyr	Ser	Val	Arg	Val	Gln	Leu	Ser	Arg	Pro	Gly	Glu	Gly	Gly
		515					520					525			
Glu	Gly	Ala	Trp	Gly	Pro	Pro	Thr	Leu	Met	Thr	Thr	Asp	Cys	Pro	Glu
	530					535					540				
Pro	Leu	Leu	Gln	Pro	Trp	Leu	Glu	Gly	Trp	His	Val	Glu	Gly	Thr	Asp
545					550					555					560
Arg	Leu	Arg	Val	Ser	Trp	Ser	Leu	Pro	Leu	Val	Pro	Gly	Pro	Leu	Val
				565					570						575
Gly	Asp	Gly	Phe	Leu	Leu	Arg	Leu	Trp	Asp	Gly	Thr	Arg	Gly	Gln	Glu
			580					585						590	
Arg	Arg	Glu	Asn	Val	Ser	Ser	Pro	Gln	Ala	Arg	Thr	Ala	Leu	Leu	Thr
		595					600					605			
Gly	Leu	Thr	Pro	Gly	Thr	His	Tyr	Gln	Leu	Asp	Val	Gln	Leu	Tyr	His
	610					615					620				
Cys	Thr	Leu	Leu	Gly	Pro	Ala	Ser	Pro	Pro	Ala	His	Val	Leu	Leu	Pro
625					630					635					640
Pro	Ser	Gly	Pro	Pro	Ala	Pro	Arg	His	Leu	His	Ala	Gln	Ala	Leu	Ser
				645					650						655
Asp	Ser	Glu	Ile	Gln	Leu	Thr	Trp	Lys	His	Pro	Glu	Ala	Leu	Pro	Gly
			660					665					670		
Pro	Ile	Ser	Lys	Tyr	Val	Val	Glu	Val	Gln	Val	Ala	Gly	Gly	Ala	Gly
		675					680						685		
Asp	Pro	Leu	Trp	Ile	Asp	Val	Asp	Arg	Pro	Glu	Glu	Thr	Ser	Thr	Ile
	690					695					700				
Ile	Arg	Gly	Leu	Asn	Ala	Ser	Thr	Arg	Tyr	Leu	Phe	Arg	Met	Arg	Ala
705					710					715					720
Ser	Ile	Gln	Gly	Leu	Gly	Asp	Trp	Ser	Asn	Thr	Val	Glu	Glu	Ser	Thr
				725					730					735	
Leu	Gly	Asn	Gly	Leu	Gln	Ala	Glu	Gly	Pro	Val	Gln	Glu	Ser	Arg	Ala
			740					745						750	
Ala	Glu	Glu	Gly	Leu	Asp	Gln	Gln	Leu	Ile	Leu	Ala	Val	Val	Gly	Ser
		755					760					765			
Val	Ser	Ala	Thr	Cys	Leu	Thr	Ile	Leu	Ala	Ala	Leu	Leu	Thr	Leu	Val
		770				775					780				
Cys	Ile	Arg	Arg	Ser	Cys	Leu	His	Arg	Arg	Arg	Thr	Phe	Thr	Tyr	Gln
785					790					795					800
Ser	Gly	Ser	Gly	Glu	Glu	Thr	Ile	Leu	Gln	Phe	Ser	Ser	Gly	Thr	Leu
				805					810					815	
Thr	Leu	Thr	Arg	Arg	Pro	Lys	Leu	Gln	Pro	Glu	Pro	Leu	Ser	Tyr	Pro
			820					825					830		
Val	Leu	Glu	Trp	Glu	Asp	Ile	Thr	Phe	Glu	Asp	Leu	Ile	Gly	Glu	Gly
			835				840					845			
Asn	Phe	Gly	Gln	Val	Ile	Arg	Ala	Met	Ile	Lys	Lys	Asp	Gly	Leu	Lys
	850					855					860				
Met	Asn	Ala	Ala	Ile	Lys	Met	Leu	Lys	Glu	Tyr	Ala	Ser	Glu	Asn	Asp
865					870					875					880
His	Arg	Asp	Phe	Ala	Gly	Glu	Leu	Glu	Val	Leu	Cys	Lys	Leu	Gly	His
				885					890					895	

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His Pro Asn Ile Ile Asn Leu Leu Gly Ala Cys Lys Asn Arg Gly Tyr
      900      905      910
Leu Tyr Ile Ala Ile Glu Tyr Ala Pro Tyr Gly Asn Leu Leu Asp Phe
      915      920      925
Leu Arg Lys Ser Arg Val Leu Glu Thr Asp Pro Ala Phe Ala Arg Glu
      930      935      940
His Gly Thr Ala Ser Thr Leu Ser Ser Arg Gln Leu Leu Arg Phe Ala
      945      950      955      960
Ser Asp Ala Ala Asn Gly Met Gln Tyr Leu Ser Glu Lys Gln Phe Ile
      965      970      975
His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Gly Glu Asn Leu Ala
      980      985      990
Ser Lys Ile Ala Asp Phe Gly Leu Ser Arg Gly Glu Glu Val Tyr Val
      995      1000      1005
Lys Lys Thr Met Gly Arg Leu Pro Val Arg Trp Met Ala Ile Glu Ser
      1010      1015      1020
Leu Asn Tyr Ser Val Tyr Thr Lys Ser Asp Val Trp Ser Phe Gly
      1025      1030      1035      1040
Val Leu Leu Trp Glu Ile Val Ser Leu Gly Gly Thr Pro Tyr Cys Gly
      1045      1050      1055
Met Thr Cys Ala Glu Leu Tyr Glu Lys Leu Pro Gln Gly Tyr Arg Met
      1060      1065      1070
Glu Gln Pro Arg Asn Cys Asp Asp Glu Val Tyr Glu Leu Met Arg Gln
      1075      1080      1085
Cys Trp Arg Asp Arg Pro Tyr Glu Arg Pro Pro Phe Ala Gln Ile Ala
      1090      1095      1100
Leu Gln Leu Gly Xaa Met Leu Glu Ala Arg Lys Ala Tyr Val Asn Met
      1105      1110      1115      1120
Ser Leu Phe Glu Asn Phe Thr Tyr Ala Gly Ile Asp Ala Thr Ala Glu
      1125      1130      1135
Glu Ala

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<210> 311
<211> 455
<212> PRT
<213> Homo sapiens

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<220>
<221> VARIANT
<222> 75
<223> Xaa = P or I

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<220>
<221> VARIANT
<222> 121
<223> Xaa = R or Q

```

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<220>
<221> VARIANT
<222> 305
<223> Xaa = P or T

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<400> 311
Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu

```

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1	5	10	15
Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro			
20	25	30	
His Leu Gly Asp Arg Glu Lys Arg Asp Ser Val Cys Pro Gln Gly Lys			
35	40	45	
Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys			
50	55	60	
Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Xaa Gly Gln Asp Thr Asp			
65	70	75	80
Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu			
85	90	95	
Arg His Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val			
100	105	110	
Glu Ile Ser Ser Cys Thr Val Asp Xaa Asp Thr Val Cys Gly Cys Arg			
115	120	125	
Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Cys Phe			
130	135	140	
Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu			
145	150	155	160
Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu			
165	170	175	
Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr			
180	185	190	
Lys Leu Cys Leu Pro Gln Ile Glu Asn Val Lys Gly Thr Glu Asp Ser			
195	200	205	
Gly Thr Thr Val Leu Leu Pro Leu Val Ile Phe Phe Gly Leu Cys Leu			
210	215	220	
Leu Ser Leu Leu Phe Ile Gly Leu Met Tyr Arg Tyr Gln Arg Trp Lys			
225	230	235	240
Ser Lys Leu Tyr Ser Ile Val Cys Gly Lys Ser Thr Pro Glu Lys Glu			
245	250	255	
Gly Glu Leu Glu Gly Thr Thr Thr Lys Pro Leu Ala Pro Asn Pro Ser			
260	265	270	
Phe Ser Pro Thr Pro Gly Phe Thr Pro Thr Leu Gly Phe Ser Pro Val			
275	280	285	
Pro Ser Ser Thr Phe Thr Ser Ser Ser Thr Tyr Thr Pro Gly Asp Cys			
290	295	300	
Xaa Asn Phe Ala Ala Pro Arg Arg Glu Val Ala Pro Pro Tyr Gln Gly			
305	310	315	320
Ala Asp Pro Ile Leu Ala Thr Ala Leu Ala Ser Asp Pro Ile Pro Asn			
325	330	335	
Pro Leu Gln Lys Trp Glu Asp Ser Ala His Lys Pro Gln Ser Leu Asp			
340	345	350	
Thr Asp Asp Pro Ala Thr Leu Tyr Ala Val Val Glu Asn Val Pro Pro			
355	360	365	
Leu Arg Trp Lys Glu Phe Val Arg Arg Leu Gly Leu Ser Asp His Glu			
370	375	380	
Ile Asp Arg Leu Glu Leu Gln Asn Gly Arg Cys Leu Arg Glu Ala Gln			
385	390	395	400
Tyr Ser Met Leu Ala Thr Trp Arg Arg Arg Thr Pro Arg Arg Glu Ala			
405	410	415	
Thr Leu Glu Leu Leu Gly Arg Val Leu Arg Asp Met Asp Leu Leu Gly			
420	425	430	
Cys Leu Glu Asp Ile Glu Glu Ala Leu Cys Gly Pro Ala Ala Leu Pro			
435	440	445	
Pro Ala Pro Ser Leu Leu Arg			



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450

455

<210> 312  
 <211> 461  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 187  
 <223> Xaa = V or M

<220>  
 <221> VARIANT  
 <222> 196  
 <223> Xaa = M or R

<220>  
 <221> VARIANT  
 <222> 232  
 <223> Xaa = E or K

<220>  
 <221> VARIANT  
 <222> 236  
 <223> Xaa = A or T

<220>  
 <221> VARIANT  
 <222> 264  
 <223> Xaa = L or P

<220>  
 <221> VARIANT  
 <222> 295  
 <223> Xaa = Q or R

<400> 312  
 Met Ala Pro Val Ala Val Trp Ala Ala Leu Ala Val Gly Leu Glu Leu  
 1 5 10 15  
 Trp Ala Ala Ala His Ala Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr  
 20 25 30  
 Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln  
 35 40 45  
 Thr Ala Gln Met Cys Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys  
 50 55 60  
 Val Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp  
 65 70 75 80  
 Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu Ser Cys  
 85 90 95  
 Gly Ser Arg Cys Ser Ser Asp Gln Val Glu Thr Gln Ala Cys Thr Arg  
 100 105 110  
 Glu Gln Asn Arg Ile Cys Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu  
 115 120 125  
 Ser Lys Gln Glu Gly Cys Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg

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130	135	140
Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Asp Val Val		
145	150	155
Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr		
	165	170
Asp Ile Cys Arg Pro His Gln Ile Cys Asn Xaa Val Ala Ile Pro Gly		175
	180	185
Asn Ala Ser Xaa Asp Ala Val Cys Thr Ser Thr Ser Pro Thr Arg Ser		190
	195	200
Met Ala Pro Gly Ala Val His Leu Pro Gln Pro Val Ser Thr Arg Ser		205
	210	215
Gln His Thr Gln Pro Thr Pro Xaa Pro Ser Thr Xaa Pro Ser Thr Ser		220
225	230	235
Phe Leu Leu Pro Met Gly Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly		240
	245	250
Asp Phe Ala Leu Pro Val Gly Xaa Ile Val Gly Val Thr Ala Leu Gly		255
	260	265
Leu Leu Ile Ile Gly Val Val Asn Cys Val Ile Met Thr Gln Val Lys		270
	275	280
Lys Lys Pro Leu Cys Leu Xaa Arg Glu Ala Lys Val Pro His Leu Pro		285
	290	295
Ala Asp Lys Ala Arg Gly Thr Gln Gly Pro Glu Gln Gln His Leu Leu		300
305	310	315
Ile Thr Ala Pro Ser Ser Ser Ser Ser Ser Leu Glu Ser Ser Ala Ser		320
	325	330
Ala Leu Asp Arg Arg Ala Pro Thr Arg Asn Gln Pro Gln Ala Pro Gly		335
	340	345
Val Glu Ala Ser Gly Ala Gly Glu Ala Arg Ala Ser Thr Gly Ser Ser		350
	355	360
Asp Ser Ser Pro Gly Gly His Gly Thr Gln Val Asn Val Thr Cys Ile		365
	370	375
Val Asn Val Cys Ser Ser Ser Asp His Ser Ser Gln Cys Ser Ser Gln		380
385	390	395
Ala Ser Ser Thr Met Gly Asp Thr Asp Ser Ser Pro Ser Glu Ser Pro		400
	405	410
Lys Asp Glu Gln Val Pro Phe Ser Lys Glu Glu Cys Ala Phe Arg Ser		415
	420	425
Gln Leu Glu Thr Pro Glu Thr Leu Leu Gly Ser Thr Glu Glu Lys Pro		430
	435	440
Leu Pro Leu Gly Val Pro Asp Ala Gly Met Lys Pro Ser		445
450	455	460

<210> 313  
 <211> 1356  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 297, 952  
 <223> Xaa = V or I

<220>  
 <221> VARIANT  
 <222> 349

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&lt;223&gt; Xaa = R or K

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 392

&lt;223&gt; Xaa = D or N

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 472

&lt;223&gt; Xaa = Q or H

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 772

&lt;223&gt; Xaa = A or T

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 787

&lt;223&gt; Xaa = R or G

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 835

&lt;223&gt; Xaa = K or N

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 848

&lt;223&gt; Xaa = V or E

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 1147

&lt;223&gt; Xaa = P or S

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 1210

&lt;223&gt; Xaa = P or A

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 1347

&lt;223&gt; Xaa = S or T

&lt;400&gt; 313

Met	Gln	Ser	Lys	Val	Leu	Leu	Ala	Val	Ala	Leu	Trp	Leu	Cys	Val	Glu
1				5					10					15	
Thr	Arg	Ala	Ala	Ser	Val	Gly	Leu	Pro	Ser	Val	Ser	Leu	Asp	Leu	Pro
			20					25					30		
Arg	Leu	Ser	Ile	Gln	Lys	Asp	Ile	Leu	Thr	Ile	Lys	Ala	Asn	Thr	Thr
		35					40					45			
Leu	Gln	Ile	Thr	Cys	Arg	Gly	Gln	Arg	Asp	Leu	Asp	Trp	Leu	Trp	Pro
		50				55					60				

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Asn	Asn	Gln	Ser	Gly	Ser	Glu	Gln	Arg	Val	Glu	Val	Thr	Glu	Cys	Ser	65	70	75	80
Asp	Gly	Leu	Phe	Cys	Lys	Thr	Leu	Thr	Ile	Pro	Lys	Val	Ile	Gly	Asn				
				85					90					95					
Asp	Thr	Gly	Ala	Tyr	Lys	Cys	Phe	Tyr	Arg	Glu	Thr	Asp	Leu	Ala	Ser				
			100					105					110						
Val	Ile	Tyr	Val	Tyr	Val	Gln	Asp	Tyr	Arg	Ser	Pro	Phe	Ile	Ala	Ser				
		115					120					125							
Val	Ser	Asp	Gln	His	Gly	Val	Val	Tyr	Ile	Thr	Glu	Asn	Lys	Asn	Lys				
		130				135					140								
Thr	Val	Val	Ile	Pro	Cys	Leu	Gly	Ser	Ile	Ser	Asn	Leu	Asn	Val	Ser				
145					150					155					160				
Leu	Cys	Ala	Arg	Tyr	Pro	Glu	Lys	Arg	Phe	Val	Pro	Asp	Gly	Asn	Arg				
				165					170					175					
Ile	Ser	Trp	Asp	Ser	Lys	Lys	Gly	Phe	Thr	Ile	Pro	Ser	Tyr	Met	Ile				
			180					185					190						
Ser	Tyr	Ala	Gly	Met	Val	Phe	Cys	Glu	Ala	Lys	Ile	Asn	Asp	Glu	Ser				
		195					200					205							
Tyr	Gln	Ser	Ile	Met	Tyr	Ile	Val	Val	Val	Val	Gly	Tyr	Arg	Ile	Tyr				
		210				215					220								
Asp	Val	Val	Leu	Ser	Pro	Ser	His	Gly	Ile	Glu	Leu	Ser	Val	Gly	Glu				
225					230					235					240				
Lys	Leu	Val	Leu	Asn	Cys	Thr	Ala	Arg	Thr	Glu	Leu	Asn	Val	Gly	Ile				
				245					250					255					
Asp	Phe	Asn	Trp	Glu	Tyr	Pro	Ser	Ser	Lys	His	Gln	His	Lys	Lys	Leu				
		260						265					270						
Val	Asn	Arg	Asp	Leu	Lys	Thr	Gln	Ser	Gly	Ser	Glu	Met	Lys	Lys	Phe				
		275					280					285							
Leu	Ser	Thr	Leu	Thr	Ile	Asp	Gly	Xaa	Thr	Arg	Ser	Asp	Gln	Gly	Leu				
		290				295				300									
Tyr	Thr	Cys	Ala	Ala	Ser	Ser	Gly	Leu	Met	Thr	Lys	Lys	Asn	Ser	Thr				
305					310					315					320				
Phe	Val	Arg	Val	His	Glu	Lys	Pro	Phe	Val	Ala	Phe	Gly	Ser	Gly	Met				
				325					330					335					
Glu	Ser	Leu	Val	Glu	Ala	Thr	Val	Gly	Glu	Arg	Val	Xaa	Ile	Pro	Ala				
		340						345					350						
Lys	Tyr	Leu	Gly	Tyr	Pro	Pro	Pro	Glu	Ile	Lys	Trp	Tyr	Lys	Asn	Gly				
		355					360					365							
Ile	Pro	Leu	Glu	Ser	Asn	His	Thr	Ile	Lys	Ala	Gly	His	Val	Leu	Thr				
		370				375				380									
Ile	Met	Glu	Val	Ser	Glu	Arg	Xaa	Thr	Gly	Asn	Tyr	Thr	Val	Ile	Leu				
385					390					395					400				
Thr	Asn	Pro	Ile	Ser	Lys	Glu	Lys	Gln	Ser	His	Val	Val	Ser	Leu	Val				
				405					410					415					
Val	Tyr	Val	Pro	Pro	Gln	Ile	Gly	Glu	Lys	Ser	Leu	Ile	Ser	Pro	Val				
			420					425					430						
Asp	Ser	Tyr	Gln	Tyr	Gly	Thr	Thr	Gln	Thr	Leu	Thr	Cys	Thr	Val	Tyr				
		435					440					445							
Ala	Ile	Pro	Pro	Pro	His	His	Ile	His	Trp	Tyr	Trp	Gln	Leu	Glu	Glu				
		450				455					460								
Glu	Cys	Ala	Asn	Glu	Pro	Ser	Xaa	Ala	Val	Ser	Val	Thr	Asn	Pro	Tyr				
465					470					475					480				
Pro	Cys	Glu	Glu	Trp	Arg	Ser	Val	Glu	Asp	Phe	Gln	Gly	Gly	Asn	Lys				
				485					490					495					
Ile	Glu	Val	Asn	Lys	Asn	Gln	Phe	Ala	Leu	Ile	Glu	Gly	Lys	Asn	Lys				
			500					505					510						

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Thr	Val	Ser	Thr	Leu	Val	Ile	Gln	Ala	Ala	Asn	Val	Ser	Ala	Leu	Tyr
		515					520					525			
Lys	Cys	Glu	Ala	Val	Asn	Lys	Val	Gly	Arg	Gly	Glu	Arg	Val	Ile	Ser
		530					535					540			
Phe	His	Val	Thr	Arg	Gly	Pro	Glu	Ile	Thr	Leu	Gln	Pro	Asp	Met	Gln
545					550					555					560
Pro	Thr	Glu	Gln	Glu	Ser	Val	Ser	Leu	Trp	Cys	Thr	Ala	Asp	Arg	Ser
				565					570					575	
Thr	Phe	Glu	Asn	Leu	Thr	Trp	Tyr	Lys	Leu	Gly	Pro	Gln	Pro	Leu	Pro
			580					585					590		
Ile	His	Val	Gly	Glu	Leu	Pro	Thr	Pro	Val	Cys	Lys	Asn	Leu	Asp	Thr
		595					600					605			
Leu	Trp	Lys	Leu	Asn	Ala	Thr	Met	Phe	Ser	Asn	Ser	Thr	Asn	Asp	Ile
		610				615					620				
Leu	Ile	Met	Glu	Leu	Lys	Asn	Ala	Ser	Leu	Gln	Asp	Gln	Gly	Asp	Tyr
625					630					635					640
Val	Cys	Leu	Ala	Gln	Asp	Arg	Lys	Thr	Lys	Lys	Arg	His	Cys	Val	Val
				645					650					655	
Arg	Gln	Leu	Thr	Val	Leu	Glu	Arg	Val	Ala	Pro	Thr	Ile	Thr	Gly	Asn
			660					665					670		
Leu	Glu	Asn	Gln	Thr	Thr	Ser	Ile	Gly	Glu	Ser	Ile	Glu	Val	Ser	Cys
		675					680					685			
Thr	Ala	Ser	Gly	Asn	Pro	Pro	Pro	Gln	Ile	Met	Trp	Phe	Lys	Asp	Asn
		690				695					700				
Glu	Thr	Leu	Val	Glu	Asp	Ser	Gly	Ile	Val	Leu	Lys	Asp	Gly	Asn	Arg
705					710					715					720
Asn	Leu	Thr	Ile	Arg	Arg	Val	Arg	Lys	Glu	Asp	Glu	Gly	Leu	Tyr	Thr
				725					730					735	
Cys	Gln	Ala	Cys	Ser	Val	Leu	Gly	Cys	Ala	Lys	Val	Glu	Ala	Phe	Phe
		740						745					750		
Ile	Ile	Glu	Gly	Ala	Gln	Glu	Lys	Thr	Asn	Leu	Glu	Ile	Ile	Ile	Leu
		755					760					765			
Val	Gly	Thr	Xaa	Val	Ile	Ala	Met	Phe	Phe	Trp	Leu	Leu	Leu	Val	Ile
		770				775					780				
Ile	Leu	Xaa	Thr	Val	Lys	Arg	Ala	Asn	Gly	Gly	Glu	Leu	Lys	Thr	Gly
785					790					795					800
Tyr	Leu	Ser	Ile	Val	Met	Asp	Pro	Asp	Glu	Leu	Pro	Leu	Asp	Glu	His
				805					810					815	
Cys	Glu	Arg	Leu	Pro	Tyr	Asp	Ala	Ser	Lys	Trp	Glu	Phe	Pro	Arg	Asp
			820					825					830		
Arg	Leu	Xaa	Leu	Gly	Lys	Pro	Leu	Gly	Arg	Gly	Ala	Phe	Gly	Gln	Xaa
			835				840					845			
Ile	Glu	Ala	Asp	Ala	Phe	Gly	Ile	Asp	Lys	Thr	Ala	Thr	Cys	Arg	Thr
		850				855				860					
Val	Ala	Val	Lys	Met	Leu	Lys	Glu	Gly	Ala	Thr	His	Ser	Glu	His	Arg
865					870					875					880
Ala	Leu	Met	Ser	Glu	Leu	Lys	Ile	Leu	Ile	His	Ile	Gly	His	His	Leu
				885					890					895	
Asn	Val	Val	Asn	Leu	Leu	Gly	Ala	Cys	Thr	Lys	Pro	Gly	Gly	Pro	Leu
			900					905					910		
Met	Val	Ile	Val	Glu	Phe	Cys	Lys	Phe	Gly	Asn	Leu	Ser	Thr	Tyr	Leu
		915					920						925		
Arg	Ser	Lys	Arg	Asn	Glu	Phe	Val	Pro	Tyr	Lys	Thr	Lys	Gly	Ala	Arg
		930				935					940				
Phe	Arg	Gln	Gly	Lys	Asp	Tyr	Xaa	Gly	Ala	Ile	Pro	Val	Asp	Leu	Lys
945					950					955					960

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```

Arg Arg Leu Asp Ser Ile Thr Ser Ser Gln Ser Ser Ala Ser Ser Gly
          965          970          975
Phe Val Glu Glu Lys Ser Leu Ser Asp Val Glu Glu Glu Ala Pro
          980          985          990
Glu Asp Leu Tyr Lys Asp Phe Leu Thr Leu Glu His Leu Ile Cys Tyr
          995          1000          1005
Ser Phe Gln Val Ala Lys Gly Met Glu Phe Leu Ala Ser Arg Lys Cys
          1010          1015          1020
Ile His Arg Asp Leu Ala Ala Arg Asn Ile Leu Leu Ser Glu Lys Asn
          1025          1030          1035          1040
Val Val Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp Ile Tyr Lys Asp
          1045          1050          1055
Pro Asp Tyr Val Arg Lys Gly Asp Ala Arg Leu Pro Leu Lys Trp Met
          1060          1065          1070
Ala Pro Glu Thr Ile Phe Asp Arg Val Tyr Thr Ile Gln Ser Asp Val
          1075          1080          1085
Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Ser Leu Gly Ala Ser
          1090          1095          1100
Pro Tyr Pro Gly Val Lys Ile Asp Glu Glu Phe Cys Arg Arg Leu Lys
          1105          1110          1115          1120
Glu Gly Thr Arg Met Arg Ala Pro Asp Tyr Thr Thr Pro Glu Met Tyr
          1125          1130          1135
Gln Thr Met Leu Asp Cys Trp His Gly Glu Xaa Ser Gln Arg Pro Thr
          1140          1145          1150
Phe Ser Glu Leu Val Glu His Leu Gly Asn Leu Leu Gln Ala Asn Ala
          1155          1160          1165
Gln Gln Asp Gly Lys Asp Tyr Ile Val Leu Pro Ile Ser Glu Thr Leu
          1170          1175          1180
Ser Met Glu Glu Asp Ser Gly Leu Ser Leu Pro Thr Ser Pro Val Ser
          1185          1190          1195          1200
Cys Met Glu Glu Glu Val Cys Asp Xaa Lys Phe His Tyr Asp Asn
          1205          1210          1215
Thr Ala Gly Ile Ser Gln Tyr Leu Gln Asn Ser Lys Arg Lys Ser Arg
          1220          1225          1230
Pro Val Ser Val Lys Thr Phe Glu Asp Ile Pro Leu Glu Glu Pro Glu
          1235          1240          1245
Val Lys Val Ile Pro Asp Asp Asn Gln Thr Asp Ser Gly Met Val Leu
          1250          1255          1260
Ala Ser Glu Glu Leu Lys Thr Leu Glu Asp Arg Thr Lys Leu Ser Pro
          1265          1270          1275          1280
Ser Phe Gly Gly Met Val Pro Ser Lys Ser Arg Glu Ser Val Ala Ser
          1285          1290          1295
Glu Gly Ser Asn Gln Thr Ser Gly Tyr Gln Ser Gly Tyr His Ser Asp
          1300          1305          1310
Asp Thr Asp Thr Thr Val Tyr Ser Ser Glu Glu Ala Glu Leu Leu Lys
          1315          1320          1325
Leu Ile Glu Ile Gly Val Gln Thr Gly Ser Thr Ala Gln Ile Leu Gln
          1330          1335          1340
Pro Asp Xaa Gly Thr Thr Leu Ser Ser Pro Pro Val
          1345          1350          1355

```

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<210> 314
<211> 1298
<212> PRT
<213> Homo sapiens

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<220>  
<221> VARIANT  
<222> 24, 134  
<223> Xaa = D or G

<220>  
<221> VARIANT  
<222> 149  
<223> Xaa = N or D

<220>  
<221> VARIANT  
<222> 494  
<223> Xaa = T or A

<220>  
<221> VARIANT  
<222> 854  
<223> Xaa = G or S

<220>  
<221> VARIANT  
<222> 890  
<223> Xaa = Q or H

<220>  
<221> VARIANT  
<222> 915  
<223> Xaa = A or P

<220>  
<221> VARIANT  
<222> 916  
<223> Xaa = C or W

<220>  
<221> VARIANT  
<222> 933  
<223> Xaa = G or R

<220>  
<221> VARIANT  
<222> 954  
<223> Xaa = P or S

<220>  
<221> VARIANT  
<222> 1008  
<223> Xaa = P or L

<220>  
<221> VARIANT  
<222> 1041  
<223> Xaa = R or Q

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<220>  
 <221> VARIANT  
 <222> 1137  
 <223> Xaa = P or L

<220>  
 <221> VARIANT  
 <222> 1164  
 <223> Xaa = D or E

<220>  
 <221> VARIANT  
 <222> 1189  
 <223> Xaa = R or L

<220>  
 <221> VARIANT  
 <222> 1324  
 <223> Xaa = R or L

<400> 314  
 Met Gln Arg Gly Ala Ala Leu Cys Leu Arg Leu Trp Leu Cys Leu Gly  
 1 5 10 15  
 Leu Leu Asp Gly Leu Val Ser Xaa Tyr Ser Met Thr Pro Pro Thr Leu  
 20 25 30  
 Asn Ile Thr Glu Glu Ser His Val Ile Asp Thr Gly Asp Ser Leu Ser  
 35 40 45  
 Ile Ser Cys Arg Gly Gln His Pro Leu Glu Trp Ala Trp Pro Gly Ala  
 50 55 60  
 Gln Glu Ala Pro Ala Thr Gly Asp Lys Asp Ser Glu Asp Thr Gly Val  
 65 70 75 80  
 Val Arg Asp Cys Glu Gly Thr Asp Ala Arg Pro Tyr Cys Lys Val Leu  
 85 90 95  
 Leu Leu His Glu Val His Ala Asn Asp Thr Gly Ser Tyr Val Cys Tyr  
 100 105 110  
 Tyr Lys Tyr Ile Lys Ala Arg Ile Glu Gly Thr Thr Ala Ala Ser Ser  
 115 120 125  
 Tyr Val Phe Val Arg Xaa Phe Glu Gln Pro Phe Ile Asn Lys Pro Asp  
 130 135 140  
 Thr Leu Leu Val Xaa Arg Lys Asp Ala Met Trp Val Pro Cys Leu Val  
 145 150 155 160  
 Ser Ile Pro Gly Leu Asn Val Thr Leu Arg Ser Gln Ser Ser Val Leu  
 165 170 175  
 Trp Pro Asp Gly Gln Glu Val Val Trp Asp Asp Arg Arg Gly Met Leu  
 180 185 190  
 Val Ser Thr Pro Leu Leu His Asp Ala Leu Tyr Leu Gln Cys Glu Thr  
 195 200 205  
 Thr Trp Gly Asp Gln Asp Phe Leu Ser Asn Pro Phe Leu Val His Ile  
 210 215 220  
 Thr Gly Asn Glu Leu Tyr Asp Ile Gln Leu Leu Pro Arg Lys Ser Leu  
 225 230 235 240  
 Glu Leu Leu Val Gly Glu Lys Leu Val Leu Asn Cys Thr Val Trp Ala  
 245 250 255  
 Glu Phe Asn Ser Gly Val Thr Phe Asp Trp Asp Tyr Pro Gly Lys Gln  
 260 265 270  
 Ala Glu Arg Gly Lys Trp Val Pro Glu Arg Arg Ser Gln Gln Thr His



		275						280						285					
Thr	Glu	Leu	Ser	Ser	Ile	Leu	Thr	Ile	His	Asn	Val	Ser	Gln	His	Asp				
	290					295					300								
Leu	Gly	Ser	Tyr	Val	Cys	Lys	Ala	Asn	Asn	Gly	Ile	Gln	Arg	Phe	Arg				
305					310					315					320				
Glu	Ser	Thr	Glu	Val	Ile	Val	His	Glu	Asn	Pro	Phe	Ile	Ser	Val	Glu				
				325					330					335					
Trp	Leu	Lys	Gly	Pro	Ile	Leu	Glu	Ala	Thr	Ala	Gly	Asp	Glu	Leu	Val				
			340					345					350						
Lys	Leu	Pro	Val	Lys	Leu	Ala	Ala	Tyr	Pro	Pro	Pro	Glu	Phe	Gln	Trp				
	355					360						365							
Tyr	Lys	Asp	Gly	Lys	Ala	Leu	Ser	Gly	Arg	His	Ser	Pro	His	Ala	Leu				
	370					375					380								
Val	Leu	Lys	Glu	Val	Thr	Glu	Ala	Ser	Thr	Gly	Thr	Tyr	Thr	Leu	Ala				
385					390					395					400				
Leu	Trp	Asn	Ser	Ala	Ala	Gly	Leu	Arg	Arg	Asn	Ile	Ser	Leu	Glu	Leu				
				405					410					415					
Val	Val	Asn	Val	Pro	Pro	Gln	Ile	His	Glu	Lys	Glu	Ala	Ser	Ser	Pro				
			420					425					430						
Ser	Ile	Tyr	Ser	Arg	His	Ser	Arg	Gln	Ala	Leu	Thr	Cys	Thr	Ala	Tyr				
	435					440						445							
Gly	Val	Pro	Leu	Pro	Leu	Ser	Ile	Gln	Trp	His	Trp	Arg	Pro	Trp	Thr				
	450					455					460								
Pro	Cys	Lys	Met	Phe	Ala	Gln	Arg	Ser	Leu	Arg	Arg	Arg	Gln	Gln	Gln				
465					470					475					480				
Asp	Leu	Met	Pro	Gln	Cys	Arg	Asp	Trp	Arg	Ala	Val	Thr	Xaa	Gln	Asp				
				485					490					495					
Ala	Val	Asn	Pro	Ile	Glu	Ser	Leu	Asp	Thr	Trp	Thr	Glu	Phe	Val	Glu				
			500					505					510						
Gly	Lys	Asn	Lys	Thr	Val	Ser	Lys	Leu	Val	Ile	Gln	Asn	Ala	Asn	Val				
	515						520					525							
Ser	Ala	Met	Tyr	Lys	Cys	Val	Val	Ser	Asn	Lys	Val	Gly	Gln	Asp	Glu				
	530					535					540								
Arg	Leu	Ile	Tyr	Phe	Tyr	Val	Thr	Thr	Ile	Pro	Asp	Gly	Phe	Thr	Ile				
545					550					555					560				
Glu	Ser	Lys	Pro	Ser	Glu	Glu	Leu	Leu	Glu	Gly	Gln	Pro	Val	Leu	Leu				
				565					570					575					
Ser	Cys	Gln	Ala	Asp	Ser	Tyr	Lys	Tyr	Glu	His	Leu	Arg	Trp	Tyr	Arg				
			580					585					590						
Leu	Asn	Leu	Ser	Thr	Leu	His	Asp	Ala	His	Gly	Asn	Pro	Leu	Leu	Leu				
	595						600					605							
Asp	Cys	Lys	Asn	Val	His	Leu	Phe	Ala	Thr	Pro	Leu	Ala	Ala	Ser	Leu				
	610					615					620								
Glu	Glu	Val	Ala	Pro	Gly	Ala	Arg	His	Ala	Thr	Leu	Ser	Leu	Ser	Ile				
625					630														

					725					730					735	
Arg	Val	Arg	Glu	Glu	Asp	Ala	Gly	Pro	Tyr	Leu	Cys	Ser	Val	Cys	Arg	
			740					745					750			
Pro	Lys	Gly	Cys	Val	Asn	Ser	Ser	Ala	Ser	Val	Ala	Val	Glu	Gly	Ser	
		755					760					765				
Glu	Asp	Lys	Gly	Ser	Met	Glu	Ile	Val	Ile	Leu	Val	Gly	Thr	Gly	Val	
	770					775					780					
Ile	Ala	Val	Phe	Phe	Trp	Val	Leu	Leu	Leu	Leu	Ile	Phe	Cys	Asn	Met	
785					790					795					800	
Arg	Arg	Pro	Ala	His	Ala	Asp	Ile	Lys	Thr	Gly	Tyr	Leu	Ser	Ile	Ile	
				805					810					815		
Met	Asp	Pro	Gly	Glu	Val	Pro	Leu	Glu	Glu	Gln	Cys	Glu	Tyr	Leu	Ser	
			820					825					830			
Tyr	Asp	Ala	Ser	Gln	Trp	Glu	Phe	Pro	Arg	Glu	Arg	Leu	His	Leu	Gly	
		835					840					845				
Arg	Val	Leu	Gly	Tyr	Xaa	Ala	Phe	Gly	Lys	Val	Val	Glu	Ala	Ser	Ala	
	850					855					860					
Phe	Gly	Ile	His	Lys	Gly	Ser	Ser	Cys	Asp	Thr	Val	Ala	Val	Lys	Met	
865					870					875					880	
Leu	Lys	Glu	Gly	Ala	Thr	Ala	Ser	Glu	Xaa	Arg	Ala	Leu	Met	Ser	Glu	
				885					890					895		
Leu	Lys	Ile	Leu	Ile	His	Ile	Gly	Asn	His	Leu	Asn	Val	Val	Asn	Leu	
			900					905					910			
Leu	Gly	Xaa	Xaa	Thr	Lys	Pro	Gln	Gly	Pro	Leu	Met	Val	Ile	Val	Glu	
		915					920					925				
Phe	Cys	Lys	Tyr	Xaa	Asn	Leu	Ser	Asn	Phe	Leu	Arg	Ala	Lys	Arg	Asp	
	930				935						940					
Ala	Phe	Ser	Pro	Cys	Ala	Glu	Lys	Ser	Xaa	Glu	Gln	Arg	Gly	Arg	Phe	
945					950					955					960	
Arg	Ala	Met	Val	Glu	Leu	Ala	Arg	Leu	Asp	Arg	Arg	Arg	Pro	Gly	Ser	
				965					970					975		
Ser	Asp	Arg	Val	Leu	Phe	Ala	Arg	Phe	Ser	Lys	Thr	Glu	Gly	Gly	Ala	
			980					985						990		
Arg	Arg	Ala	Ser	Pro	Asp	Gln	Glu	Ala	Glu	Asp	Leu	Trp	Leu	Ser	Xaa	
			995				1000					1005				
Leu	Thr	Met	Glu	Asp	Leu	Val	Cys	Tyr	Ser	Phe	Gln	Val	Ala	Arg	Gly	
	1010					1015					1020					
Met	Glu	Phe	Leu	Ala	Ser	Arg	Lys	Cys	Ile	His	Arg	Asp	Leu	Ala	Ala	
1025					1030					1035					1040	
Xaa	Asn	Ile	Leu	Leu	Ser	Glu	Ser	Asp	Val	Val	Lys	Ile	Cys	Asp	Phe	
				1045					1050					1055		
Gly	Leu	Ala	Arg	Asp	Ile	Tyr	Lys	Asp	Pro	Asp	Tyr	Val	Arg	Lys	Gly	
			1060													

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1170		1175		1180
Cys Met Ala Pro Xaa Ser Ser Gln Ser Ser Glu Glu Gly Ser Phe Ser				
1185		1190		1195
Gln Val Ser Thr Met Ala Leu His Ile Ala Gln Ala Asp Ala Glu Asp				1200
	1205		1210	1215
Ser Pro Pro Ser Leu Gln Arg His Ser Leu Ala Ala Arg Tyr Tyr Asn				
	1220		1225	1230
Trp Val Ser Phe Pro Gly Cys Leu Ala Arg Gly Ala Glu Thr Arg Gly				
	1235		1240	1245
Ser Ser Arg Met Lys Thr Phe Glu Glu Phe Pro Met Thr Pro Thr Thr				
	1250		1255	1260
Tyr Lys Gly Ser Val Asp Asn Gln Thr Asp Ser Gly Met Val Leu Ala				
1265		1270		1275
Ser Glu Glu Phe Glu Gln Ile Glu Ser Arg His Arg Gln Glu Ser Gly				1280
	1285		1290	1295
Phe Arg				

<210> 315  
 <211> 27  
 <212> DNA  
 <213> synthetic

<400> 315  
 ccatgggcgg cggcggctct gccatgg

27

<210> 316  
 <211> 42  
 <212> DNA  
 <213> synthetic

<400> 316  
 ccatgggcgg cggcggctct ggccggcggc gctctgccat gg

42

<210> 317  
 <211> 75  
 <212> DNA  
 <213> synthetic

<400> 317  
 ccatggcctc gtcgtcgtcg ggctcgtcgt cgtcgggctc gtcgtcgtcg ggctcgtcgt  
 cgtcgggcgc catgg

60

75

<210> 318  
 <211> 45  
 <212> DNA  
 <213> synthetic

<400> 318  
 ccatggcctc gtcgtcgtcg ggctcgtcgt cgtcgggcgc catgg

45

<210> 319  
 <211> 8  
 <212> PRT  
 <213> synthetic

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&lt;400&gt; 319

Ala Ala Pro Ala Ala Ala Pro Ala

1 5

&lt;210&gt; 320

&lt;211&gt; 419

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 320

```

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
1      5      10      15
Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
20      25      30
Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
35      40      45
Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
50      55      60
Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65      70      75      80
Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
85      90      95
Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
100     105     110
Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
115     120     125
Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
130     135     140
Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
145     150     155     160
Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
165     170     175
Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
180     185     190
His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
195     200     205
Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
210     215     220
Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
225     230     235     240
Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
245     250     255
His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
260     265     270
Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
275     280     285
Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
290     295     300
Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305     310     315     320
Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
325     330     335
Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val
340     345     350
Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser

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          355          360          365
Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
  370          375          380
Leu Ala Pro Leu Asp Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
  385          390          395          400
Gly Arg Gly Pro Ser Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
          405          410          415
Tyr Glu Gly

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<210> 321  
 <211> 79  
 <212> PRT  
 <213> Homo sapiens

```

<400> 321
Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu
  1          5          10          15
Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
          20          25          30
Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
          35          40          45
Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro
  50          55          60
Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
  65          70          75

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<210> 322  
 <211> 419  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 342  
 <223> Xaa= Thr or Ser

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<400> 322
Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
  1          5          10          15
Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
          20          25          30
Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
          35          40          45
Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
  50          55          60
Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
  65          70          75          80
Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
          85          90          95
Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
          100          105          110
Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
          115          120          125
Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
          130          135          140
Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln

```

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```

145          150          155          160
Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
          165          170          175
Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
          180          185          190
His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
          195          200          205
Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
          210          215          220
Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
225          230          235          240
Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
          245          250          255
His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
          260          265          270
Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
          275          280          285
Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
          290          295          300
Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305          310          315          320
Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
          325          330          335
Pro Cys Ala Arg Gly Xaa His Ser Leu Pro Pro Arg Pro Ala Ala Val
          340          345          350
Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser
          355          360          365
Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
          370          375          380
Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
385          390          395          400
Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
          405          410          415
Tyr Glu Gly

```

&lt;210&gt; 323

&lt;211&gt; 419

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 345

&lt;223&gt; Xaa= Leu or Pro

&lt;400&gt; 323

```

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
1          5          10          15
Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
          20          25          30
Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
          35          40          45
Leu Tyr Gln Gly Cys Gln Val Gln Gly Asn Leu Glu Leu Thr Tyr
50          55          60
Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65          70          75          80

```

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Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu  
                   85                  90                  95  
 Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr  
                   100                  105                  110  
 Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro  
                   115                  120                  125  
 Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser  
                   130                  135                  140  
 Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln  
                   145                  150                  155                  160  
 Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn  
                   165                  170                  175  
 Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys  
                   180                  185                  190  
 His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser  
                   195                  200                  205  
 Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys  
                   210                  215                  220  
 Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys  
                   225                  230                  235                  240  
 Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu  
                   245                  250                  255  
 His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val  
                   260                  265                  270  
 Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg  
                   275                  280                  285  
 Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu  
                   290                  295                  300  
 Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln  
                   305                  310                  315                  320  
 Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys  
                   325                  330                  335  
 Pro Cys Ala Arg Gly Thr His Ser Xaa Pro Pro Arg Pro Ala Ala Val  
                   340                  345                  350  
 Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser  
                   355                  360                  365  
 Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro  
                   370                  375                  380  
 Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val  
                   385                  390                  395                  400  
 Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg  
                   405                  410                  415  
 Tyr Glu Gly

&lt;210&gt; 324

&lt;211&gt; 419

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 346

&lt;223&gt; Xaa= Pro or Leu

&lt;400&gt; 324

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu

1					5					10					15				
Pro	Pro	Gly	Ala	Ala	Ser	Thr	Gln	Val	Cys	Thr	Gly	Thr	Asp	Met	Lys				
			20					25					30						
Leu	Arg	Leu	Pro	Ala	Ser	Pro	Glu	Thr	His	Leu	Asp	Met	Leu	Arg	His				
		35					40					45							
Leu	Tyr	Gln	Gly	Cys	Gln	Val	Val	Gln	Gly	Asn	Leu	Glu	Leu	Thr	Tyr				
		50				55					60								
Leu	Pro	Thr	Asn	Ala	Ser	Leu	Ser	Phe	Leu	Gln	Asp	Ile	Gln	Glu	Val				
65					70					75					80				
Gln	Gly	Tyr	Val	Leu	Ile	Ala	His	Asn	Gln	Val	Arg	Gln	Val	Pro	Leu				
			85						90					95					
Gln	Arg	Leu	Arg	Ile	Val	Arg	Gly	Thr	Gln	Leu	Phe	Glu	Asp	Asn	Tyr				
			100					105					110						
Ala	Leu	Ala	Val	Leu	Asp	Asn	Gly	Asp	Pro	Leu	Asn	Asn	Thr	Thr	Pro				
		115					120					125							
Val	Thr	Gly	Ala	Ser	Pro	Gly	Gly	Leu	Arg	Glu	Leu	Gln	Leu	Arg	Ser				
		130				135					140								
Leu	Thr	Glu	Ile	Leu	Lys	Gly	Gly	Val	Leu	Ile	Gln	Arg	Asn	Pro	Gln				
145					150					155					160				
Leu	Cys	Tyr	Gln	Asp	Thr	Ile	Leu	Trp	Lys	Asp	Ile	Phe	His	Lys	Asn				
				165					170					175					
Asn	Gln	Leu	Ala	Leu	Thr	Leu	Ile	Asp	Thr	Asn	Arg	Ser	Arg	Ala	Cys				
			180					185					190						
His	Pro	Cys	Ser	Pro	Met	Cys	Lys	Gly	Ser	Arg	Cys	Trp	Gly	Glu	Ser				
		195					200					205							
Ser	Glu	Asp	Cys	Gln	Ser	Leu	Thr	Arg	Thr	Val	Cys	Ala	Gly	Gly	Cys				
		210				215					220								
Ala	Arg	Cys	Lys	Gly	Pro	Leu	Pro	Thr	Asp	Cys	Cys	His	Glu	Gln	Cys				
225					230				235						240				
Ala	Ala	Gly	Cys	Thr	Gly	Pro	Lys	His	Ser	Asp	Cys	Leu	Ala	Cys	Leu				
			245						250					255					
His	Phe	Asn	His	Ser	Gly	Ile	Cys	Glu	Leu	His	Cys	Pro	Ala	Leu	Val				
			260					265					270						
Thr	Tyr	Asn	Thr	Asp	Thr	Phe	Glu	Ser	Met	Pro	Asn	Pro	Glu	Gly	Arg				
		275					280					285							
Tyr	Thr	Phe	Gly	Ala	Ser	Cys	Val	Thr	Ala	Cys	Pro	Tyr	Asn	Tyr	Leu				
		290				295					300								
Ser	Thr	Asp	Val	Gly	Ser	Cys	Thr	Leu	Val	Cys	Pro	Leu	His	Asn	Gln				
305					310					315					320				
Glu	Val	Thr	Ala	Glu	Asp	Gly	Thr	Gln	Arg	Cys	Glu	Lys	Cys	Ser	Lys				
			325						330					335					
Pro	Cys	Ala	Arg																

```
<210> 325
<211> 419
<212> PRT
```



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&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 356

&lt;223&gt; Xaa= Leu or Gln

&lt;400&gt; 325

```

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1           5           10           15
Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
           20           25           30
Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
           35           40           45
Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
           50           55           60
Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
           65           70           75           80
Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
           85           90           95
Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
           100          105          110
Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
           115          120          125
Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
           130          135          140
Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
           145          150          155          160
Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
           165          170          175
Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
           180          185          190
His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
           195          200          205
Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
           210          215          220
Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
           225          230          235          240
Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
           245          250          255
His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
           260          265          270
Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
           275          280          285
Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
           290          295          300
Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
           305          310          315          320
Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
           325          330          335
Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val
           340          345          350
Pro Val Pro Xaa Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser
           355          360          365
Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
           370          375          380

```

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Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val  
 385 390 395 400  
 Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg  
 405 410 415

Tyr Glu Gly

&lt;210&gt; 326

&lt;211&gt; 419

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 358

&lt;223&gt; Xaa= Met or Leu

&lt;400&gt; 326

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu  
 1 5 10 15  
 Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys  
 20 25 30  
 Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His  
 35 40 45  
 Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr  
 50 55 60  
 Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val  
 65 70 75 80  
 Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu  
 85 90 95  
 Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr  
 100 105 110  
 Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro  
 115 120 125  
 Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser  
 130 135 140  
 Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln  
 145 150 155 160  
 Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn  
 165 170 175  
 Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys  
 180 185 190  
 His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser  
 195 200 205  
 Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys  
 210 215 220  
 Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys  
 225 230 235 240  
 Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu  
 245 250 255  
 His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val  
 260 265 270  
 Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg  
 275 280 285  
 Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu  
 290 295 300  
 Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln

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```

305          310          315          320
Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
          325          330          335
Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val
          340          345          350
Pro Val Pro Leu Arg Xaa Gln Pro Gly Pro Ala His Pro Val Leu Ser
          355          360          365
Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
          370          375          380
Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
          385          390          395          400
Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
          405          410          415
Tyr Glu Gly

```

&lt;210&gt; 327

&lt;211&gt; 419

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 361

&lt;223&gt; Xaa= Gly, Asp, Ala, or Val

&lt;400&gt; 327

```

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
  1          5          10          15
Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
          20          25          30
Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
          35          40          45
Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
          50          55          60
Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
          65          70          75          80
Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
          85          90          95
Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
          100          105          110
Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
          115          120          125
Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
          130          135          140
Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
          145          150          155          160
Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
          165          170          175
Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
          180          185          190
His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
          195          200          205
Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
          210          215          220
Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
          225          230          235          240

```

[illegible]

```
<210> 328
<211> 419
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> VARIANT
<222> 376
<223> Xaa= Leu or Ile
```

<400> 328																
Met	Glu	Leu	Ala	Ala	Leu	Cys	Arg	Trp	Gly	Leu	Leu	Leu	Ala	Leu	Leu	
1				5					10					15		
Pro	Pro	Gly	Ala	Ala	Ser	Thr	Gln	Val	Cys	Thr	Gly	Thr	Asp	Met	Lys	
			20					25					30			
Leu	Arg	Leu	Pro	Ala	Ser	Pro	Glu	Thr	His	Leu	Asp	Met	Leu	Arg	His	
		35					40					45				
Leu	Tyr	Gln	Gly	Cys	Gln	Val	Val	Gln	Gly	Asn	Leu	Glu	Leu	Thr	Tyr	
	50					55					60					
Leu	Pro	Thr	Asn	Ala	Ser	Leu	Ser	Phe	Leu	Gln	Asp	Ile	Gln	Glu	Val	
65				70					75						80	
Gln	Gly	Tyr	Val	Leu	Ile	Ala	His	Asn	Gln	Val	Arg	Gln	Val	Pro	Leu	
				85					90					95		
Gln	Arg	Leu	Arg	Ile	Val	Arg	Gly	Thr	Gln	Leu	Phe	Glu	Asp	Asn	Tyr	
			100					105					110			
Ala	Leu	Ala	Val	Leu	Asp	Asn	Gly	Asp	Pro	Leu	Asn	Asn	Thr	Thr	Pro	
		115					120					125				
Val	Thr	Gly	Ala	Ser	Pro	Gly	Gly	Leu	Arg	Glu	Leu	Gln	Leu	Arg	Ser	
	130					135					140					
Leu	Thr	Glu	Ile	Leu	Lys	Gly	Gly	Val	Leu	Ile	Gln	Arg	Asn	Pro	Gln	
145					150					155					160	

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Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn  
 165 170 175  
 Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys  
 180 185 190  
 His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser  
 195 200 205  
 Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys  
 210 215 220  
 Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys  
 225 230 235 240  
 Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu  
 245 250 255  
 His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val  
 260 265 270  
 Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg  
 275 280 285  
 Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu  
 290 295 300  
 Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln  
 305 310 315 320  
 Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys  
 325 330 335  
 Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val  
 340 345 350  
 Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser  
 355 360 365  
 Phe Leu Arg Pro Ser Trp Asp Xaa Val Ser Ala Phe Tyr Ser Leu Pro  
 370 375 380  
 Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val  
 385 390 395 400  
 Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg  
 405 410 415  
 Tyr Glu Gly

&lt;210&gt; 329

&lt;211&gt; 419

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 394

&lt;223&gt; Xaa= Pro or Arg

&lt;400&gt; 329

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu  
 1 5 10 15  
 Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys  
 20 25 30  
 Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His  
 35 40 45  
 Leu Tyr Gln Gly Cys Gln Val Gln Gly Asn Leu Glu Leu Thr Tyr  
 50 55 60  
 Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val  
 65 70 75 80  
 Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu

```
<400> 330
Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1             5             10            15
```

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```

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
      20      25      30
Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
      35      40      45
Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
      50      55      60
Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
      65      70      75      80
Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
      85      90      95
Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
      100      105      110
Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
      115      120      125
Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
      130      135      140
Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
      145      150      155      160
Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
      165      170      175
Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
      180      185      190
His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
      195      200      205
Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
      210      215      220
Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
      225      230      235      240
Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
      245      250      255
His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
      260      265      270
Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
      275      280      285
Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
      290      295      300
Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
      305      310      315      320
Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
      325      330      335
Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val
      340      345      350
Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser
      355      360      365
Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
      370      375      380
Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
      385      390      395      400
Gly Arg Gly Xaa Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
      405      410      415
Tyr Glu Gly

```

&lt;210&gt; 331

&lt;211&gt; 419

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

- 414 -

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 413

&lt;223&gt; Xaa= Asp or Asn

&lt;400&gt; 331

```

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1          5          10          15
Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
          20          25          30
Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
          35          40          45
Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
 50          55          60
Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65          70          75          80
Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
          85          90          95
Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
          100          105          110
Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
          115          120          125
Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
          130          135          140
Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
145          150          155          160
Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
          165          170          175
Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
          180          185          190
His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
          195          200          205
Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
          210          215          220
Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
225          230          235          240
Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
          245          250          255
His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
          260          265          270
Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
          275          280          285
Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
          290          295          300
Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305          310          315          320
Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
          325          330          335
Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val
          340          345          350
Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser
          355          360          365
Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
          370          375          380
Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val

```



[illegible]

```
<210> 332
<211> 419
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> VARIANT
<222> 357
<223> Xaa= Arg or Cys
```

<400>	332															
Met	Glu	Leu	Ala	Ala	Leu	Cys	Arg	Trp	Gly	Leu	Leu	Leu	Ala	Leu	Leu	
1				5					10					15		
Pro	Pro	Gly	Ala	Ala	Ser	Thr	Gln	Val	Cys	Thr	Gly	Thr	Asp	Met	Lys	
			20					25					30			
Leu	Arg	Leu	Pro	Ala	Ser	Pro	Glu	Thr	His	Leu	Asp	Met	Leu	Arg	His	
		35					40					45				
Leu	Tyr	Gln	Gly	Cys	Gln	Val	Val	Gln	Gly	Asn	Leu	Glu	Leu	Thr	Tyr	
	50					55					60					
Leu	Pro	Thr	Asn	Ala	Ser	Leu	Ser	Phe	Leu	Gln	Asp	Ile	Gln	Glu	Val	
65					70					75					80	
Gln	Gly	Tyr	Val	Leu	Ile	Ala	His	Asn	Gln	Val	Arg	Gln	Val	Pro	Leu	
				85					90					95		
Gln	Arg	Leu	Arg	Ile	Val	Arg	Gly	Thr	Gln	Leu	Phe	Glu	Asp	Asn	Tyr	
			100					105					110			
Ala	Leu	Ala	Val	Leu	Asp	Asn	Gly	Asp	Pro	Leu	Asn	Asn	Thr	Thr	Pro	
		115					120					125				
Val	Thr	Gly	Ala	Ser	Pro	Gly	Gly	Leu	Arg	Glu	Leu	Gln	Leu	Arg	Ser	
		130				135					140					
Leu	Thr	Glu	Ile	Leu	Lys	Gly	Gly	Val	Leu	Ile	Gln	Arg	Asn	Pro	Gln	
145					150					155					160	
Leu	Cys	Tyr	Gln	Asp	Thr	Ile	Leu	Trp	Lys	Asp	Ile	Phe	His	Lys	Asn	
				165					170					175		
Asn	Gln	Leu	Ala	Leu	Thr	Leu	Ile	Asp	Thr	Asn	Arg	Ser	Arg	Ala	Cys	
			180					185					190			
His	Pro	Cys	Ser	Pro	Met	Cys	Lys	Gly	Ser	Arg	Cys	Trp	Gly	Glu	Ser	
		195					200					205				
Ser	Glu	Asp	Cys	Gln	Ser	Leu	Thr	Arg	Thr	Val	Cys	Ala	Gly	Gly	Cys	
		210				215					220					
Ala	Arg	Cys	Lys	Gly	Pro	Leu	Pro	Thr	Asp	Cys	Cys	His	Glu	Gln	Cys	
225					230				235						240	
Ala	Ala	Gly	Cys	Thr	Gly	Pro	Lys	His	Ser	Asp	Cys	Leu	Ala	Cys	Leu	
				245					250					255		
His	Phe	Asn	His	Ser	Gly	Ile	Cys	Glu	Leu	His	Cys	Pro	Ala	Leu	Val	
			260					265					270			
Thr	Tyr	Asn	Thr	Asp	Thr	Phe	Glu	Ser	Met	Pro	Asn	Pro	Glu	Gly	Arg	
		275					280					285				
Tyr	Thr	Phe	Gly	Ala	Ser	Cys	Val	Thr	Ala	Cys	Pro	Tyr	Asn	Tyr	Leu	
		290				295					300					
Ser	Thr	Asp	Val	Gly	Ser	Cys	Thr	Leu	Val	Cys	Pro	Leu	His	Asn	Gln	
305					310					315					320	

[illegible]

```
<220>  
<221> VARIANT  
<222> 371  
<223> Xaa= Arg or Ile
```

[illegible]

			245					250					255				
His	Phe	Asn	His	Ser	Gly	Ile	Cys	Glu	Leu	His	Cys	Pro	Ala	Leu	Val		
			260					265					270				
Thr	Tyr	Asn	Thr	Asp	Thr	Phe	Glu	Ser	Met	Pro	Asn	Pro	Glu	Gly	Arg		
			275					280					285				
Tyr	Thr	Phe	Gly	Ala	Ser	Cys	Val	Thr	Ala	Cys	Pro	Tyr	Asn	Tyr	Leu		
			290					295					300				
Ser	Thr	Asp	Val	Gly	Ser	Cys	Thr	Leu	Val	Cys	Pro	Leu	His	Asn	Gln		
305			310					315					320				
Glu	Val	Thr	Ala	Glu	Asp	Gly	Thr	Gln	Arg	Cys	Glu	Lys	Cys	Ser	Lys		
			325					330					335				
Pro	Cys	Ala	Arg	Gly	Thr	His	Ser	Leu	Pro	Pro	Arg	Pro	Ala	Ala	Val		
			340					345					350				
Pro	Val	Pro	Leu	Arg	Met	Gln	Pro	Gly	Pro	Ala	His	Pro	Val	Leu	Ser		
			355					360					365				
Phe	Leu	Xaa	Pro	Ser	Trp	Asp	Leu	Val	Ser	Ala	Phe	Tyr	Ser	Leu	Pro		
			370					375					380				
Leu	Ala	Pro	Leu	Ser	Pro	Thr	Ser	Val	Pro	Ile	Ser	Pro	Val	Ser	Val		
385			390					395					400				
Gly	Arg	Gly	Pro	Asp	Pro	Asp	Ala	His	Val	Ala	Val	Asp	Leu	Ser	Arg		
			405					410					415				
Tyr	Glu	Gly															

```
<210> 334
<211> 79
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> VARIANT
<222> 2
<223> Xaa= Thr or Ser
```

<400> 334															
Gly	Xaa	His	Ser	Leu	Pro	Pro	Arg	Pro	Ala	Ala	Val	Pro	Val	Pro	Leu
1				5					10					15	
Arg	Met	Gln	Pro	Gly	Pro	Ala	His	Pro	Val	Leu	Ser	Phe	Leu	Arg	Pro
			20					25					30		
Ser	Trp	Asp	Leu	Val	Ser	Ala	Phe	Tyr	Ser	Leu	Pro	Leu	Ala	Pro	Leu
		35					40					45			
Ser	Pro	Thr	Ser	Val	Pro	Ile	Ser	Pro	Val	Ser	Val	Gly	Arg	Gly	Pro
	50					55					60				
Asp	Pro	Asp	Ala	His	Val	Ala	Val	Asp	Leu	Ser	Arg	Tyr	Glu	Gly	
65					70					75					

```
<210> 335
<211> 79
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> VARIANT
<222> 5
<223> Xaa= Leu or Pro
```

**<400> 335**

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Gly Thr His Ser Xaa Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu  
 1 5 10 15  
 Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro  
 20 25 30  
 Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu  
 35 40 45  
 Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro  
 50 55 60  
 Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly  
 65 70 75

&lt;210&gt; 336

&lt;211&gt; 79

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 6

&lt;223&gt; Xaa= Pro or Leu

&lt;400&gt; 336

Gly Thr His Ser Leu Xaa Pro Arg Pro Ala Ala Val Pro Val Pro Leu  
 1 5 10 15  
 Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro  
 20 25 30  
 Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu  
 35 40 45  
 Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro  
 50 55 60  
 Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly  
 65 70 75

&lt;210&gt; 337

&lt;211&gt; 79

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 16

&lt;223&gt; Xaa= Leu or Gln

&lt;400&gt; 337

Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Xaa  
 1 5 10 15  
 Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro  
 20 25 30  
 Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu  
 35 40 45  
 Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro  
 50 55 60  
 Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly  
 65 70 75

&lt;210&gt; 338

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<211> 79  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 18  
 <223> Xaa= Met or Leu

<400> 338  
 Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu  
 1 5 10 15  
 Arg Xaa Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro  
 20 25 30  
 Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu  
 35 40 45  
 Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro  
 50 55 60  
 Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly  
 65 70 75

<210> 339  
 <211> 79  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 21  
 <223> Xaa= Gly, Asp, Ala, or Val

<400> 339  
 Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu  
 1 5 10 15  
 Arg Met Gln Pro Xaa Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro  
 20 25 30  
 Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu  
 35 40 45  
 Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro  
 50 55 60  
 Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly  
 65 70 75

<210> 340  
 <211> 79  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 36  
 <223> Xaa= Leu or Ile

<400> 340  
 Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu

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```

      1           5           10           15
Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
      20           25           30
Ser Trp Asp Xaa Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
      35           40           45
Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro
      50           55           60
Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
      65           70           75

```

<210> 341  
 <211> 79  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 54  
 <223> Xaa= Pro or Arg

```

<400> 341
Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu
      1           5           10           15
Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
      20           25           30
Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
      35           40           45
Ser Pro Thr Ser Val Xaa Ile Ser Pro Val Ser Val Gly Arg Gly Pro
      50           55           60
Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
      65           70           75

```

<210> 342  
 <211> 79  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 64  
 <223> Xaa= Pro or Leu

```

<400> 342
Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu
      1           5           10           15
Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
      20           25           30
Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
      35           40           45
Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Xaa
      50           55           60
Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
      65           70           75

```

<210> 343  
 <211> 79

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<212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 73  
 <223> Xaa= Asp or Asn

<400> 343  
 Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu  
 1 5 10 15  
 Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro  
 20 25 30  
 Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu  
 35 40 45  
 Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro  
 50 55 60  
 Asp Pro Asp Ala His Val Ala Val Xaa Leu Ser Arg Tyr Glu Gly  
 65 70 75

<210> 344  
 <211> 79  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 17  
 <223> Xaa= Arg or Cys

<400> 344  
 Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu  
 1 5 10 15  
 Xaa Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro  
 20 25 30  
 Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu  
 35 40 45  
 Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro  
 50 55 60  
 Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly  
 65 70 75

<210> 345  
 <211> 79  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> 31  
 <223> Xaa= Arg or Ile

<400> 345  
 Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu  
 1 5 10 15  
 Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Xaa Pro

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	20		25		30										
Ser	Trp	Asp	Leu	Val	Ser	Ala	Phe	Tyr	Ser	Leu	Pro	Leu	Ala	Pro	Leu
	35		40		45										
Ser	Pro	Thr	Ser	Val	Pro	Ile	Ser	Pro	Val	Ser	Val	Gly	Arg	Gly	Pro
	50		55		60										
Asp	Pro	Asp	Ala	His	Val	Ala	Val	Asp	Leu	Ser	Arg	Tyr	Glu	Gly	
65					70					75					

<210> 346  
 <211> 240  
 <212> DNA  
 <213> Homo sapiens

<400> 346  
 ggtaccact cactgcccc gaggccagct gcagttcctg tccctctgcg catgcagcct 60  
 ggcccagccc accctgtcct atccttcctc agaccctctt gggacctagt ctctgccttc 120  
 tactctctac ccctggcccc cctcagccct acaagtgtcc ctatatcccc tgtcagtgtg 180  
 gggagggggc cggaccctga tgctcatgtg gctggtgacc tgtcccggta tgaaggctga 240

<210> 347  
 <211> 240  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> 4  
 <223> n= T

<400> 347  
 ggtaccact cactgcccc gaggccagct gcagttcctg tccctctgcg catgcagcct 60  
 ggcccagccc accctgtcct atccttcctc agaccctctt gggacctagt ctctgccttc 120  
 tactctctac ccctggcccc cctcagccct acaagtgtcc ctatatcccc tgtcagtgtg 180  
 gggagggggc cggaccctga tgctcatgtg gctggtgacc tgtcccggta tgaaggctga 240

<210> 348  
 <211> 240  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> 14  
 <223> n= C

<400> 348  
 ggtaccact cacngcccc gaggccagct gcagttcctg tccctctgcg catgcagcct 60  
 ggcccagccc accctgtcct atccttcctc agaccctctt gggacctagt ctctgccttc 120  
 tactctctac ccctggcccc cctcagccct acaagtgtcc ctatatcccc tgtcagtgtg 180  
 gggagggggc cggaccctga tgctcatgtg gctggtgacc tgtcccggta tgaaggctga 240

<210> 349  
 <211> 240  
 <212> DNA  
 <213> Homo sapiens



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&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; 17

&lt;223&gt; n= T

&lt;400&gt; 349

```
ggtaccact cactgcnccc gaggccagct gcagttcctg tccctctgcg catgcagcct 60
ggcccagccc accctgtcct atccttcctc agaccctctt gggacctagt ctctgccttc 120
tactctctac ccctggcccc cctcagccct acaagtgtcc ctatatcccc tgtcagtgtg 180
gggagggggcc cggaccctga tgctcatgtg gctgttgacc tgtcccggta tgaaggctga 240
```

&lt;210&gt; 350

&lt;211&gt; 240

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; 47

&lt;223&gt; n= A

&lt;400&gt; 350

```
ggtaccact cactgcccc gaggccagct gcagttcctg tccctcngcg catgcagcct 60
ggcccagccc accctgtcct atccttcctc agaccctctt gggacctagt ctctgccttc 120
tactctctac ccctggcccc cctcagccct acaagtgtcc ctatatcccc tgtcagtgtg 180
gggagggggcc cggaccctga tgctcatgtg gctgttgacc tgtcccggta tgaaggctga 240
```

&lt;210&gt; 351

&lt;211&gt; 240

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; 54

&lt;223&gt; n= A

&lt;400&gt; 351

```
ggtaccact cactgcccc gaggccagct gcagttcctg tccctctgcg catncagcct 60
ggcccagccc accctgtcct atccttcctc agaccctctt gggacctagt ctctgccttc 120
tactctctac ccctggcccc cctcagccct acaagtgtcc ctatatcccc tgtcagtgtg 180
gggagggggcc cggaccctga tgctcatgtg gctgttgacc tgtcccggta tgaaggctga 240
```

&lt;210&gt; 352

&lt;211&gt; 240

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; 62

&lt;223&gt; n= C, T, or A

&lt;400&gt; 352

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```
ggtaccact cactgcccc gaggccagct gcagttcctg tccctctgcg catgcagcct 60
gncccagccc accctgtcct atccttcctc agaccctctt gggacctagt ctctgccttc 120
tactctctac ccctggcccc cctcagccct acaagtgtcc ctatatcccc tgtcagtgtg 180
gggagggggc cggaccctga tgctcatgtg gctgttgacc tgtcccggta tgaaggctga 240
```

```
<210> 353
<211> 240
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc_feature
<222> 106
<223> n= A
```

```
<400> 353
ggtaccact cactgcccc gaggccagct gcagttcctg tccctctgcg catgcagcct 60
ggcccagccc accctgtcct atccttcctc agaccctctt gggacctagt ctctgccttc 120
tactctctac ccctggcccc cctcagccct acaagtgtcc ctatatcccc tgtcagtgtg 180
gggagggggc cggaccctga tgctcatgtg gctgttgacc tgtcccggta tgaaggctga 240
```

```
<210> 354
<211> 240
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc_feature
<222> 161
<223> n= C
```

```
<400> 354
ggtaccact cactgcccc gaggccagct gcagttcctg tccctctgcg catgcagcct 60
ggcccagccc accctgtcct atccttcctc agaccctctt gggacctagt ctctgccttc 120
tactctctac ccctggcccc cctcagccct acaagtgtcc ntatatcccc tgtcagtgtg 180
gggagggggc cggaccctga tgctcatgtg gctgttgacc tgtcccggta tgaaggctga 240
```

```
<210> 355
<211> 240
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc_feature
<222> 191
<223> n= T
```

```
<400> 355
ggtaccact cactgcccc gaggccagct gcagttcctg tccctctgcg catgcagcct 60
ggcccagccc accctgtcct atccttcctc agaccctctt gggacctagt ctctgccttc 120
tactctctac ccctggcccc cctcagccct acaagtgtcc ctatatcccc tgtcagtgtg 180
gggagggggc nggaccctga tgctcatgtg gctgttgacc tgtcccggta tgaaggctga 240
```

```
<210> 356
```

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<211> 240  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> 217  
<223> n= C

<400> 356  
ggtaccact cactgcccc gaggccagct gcagttcctg tccctctgcg catgcagcct 60  
ggcccagccc accctgtcct atccttcctc agaccctctt gggacctagt ctctgccttc 120  
tactctctac ccctggcccc cctcagccct acaagtgtcc ctatatcccc tgtcagtgtg 180  
gggagggggcc cggaccctga tgctcatgtg gctgttnacc tgtcccggta tgaaggctga 240

<210> 357  
<211> 240  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> 17  
<223> n= T

<220>  
<221> misc\_feature  
<222> 217  
<223> n= C

<400> 357  
ggtaccact cactgcncct gaggccagct gcagttcctg tccctctgcg catgcagcct 60  
ggcccagccc accctgtcct atccttcctc agaccctctt gggacctagt ctctgccttc 120  
tactctctac ccctggcccc cctcagccct acaagtgtcc ctatatcccc tgtcagtgtg 180  
gggagggggcc cggaccctga tgctcatgtg gctgttnacc tgtcccggta tgaaggctga 240

<210> 358  
<211> 240  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> 49  
<223> n= T

<400> 358  
ggtaccact cactgcccc gaggccagct gcagttcctg tccctctgng catgcagcct 60  
ggcccagccc accctgtcct atccttcctc agaccctctt gggacctagt ctctgccttc 120  
tactctctac ccctggcccc cctcagccct acaagtgtcc ctatatcccc tgtcagtgtg 180  
gggagggggcc cggaccctga tgctcatgtg gctgttnacc tgtcccggta tgaaggctga 240

<210> 359

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<211> 240  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> 92  
<223> n= T

<400> 359  
ggtaccact cactgcccc gaggccagct gcagttcctg tccctctgcg catgcagcct 60  
ggcccagccc accctgtcct atccttcctc anaccctctt gggacctagt ctctgccttc 120  
tactctctac ccctggcccc cctcagccct acaagtgtcc ctatatcccc tgtcagtgtg 180  
gggagggggcc cggaccctga tgctcatgtg gctgttnacc tgtcccggta tgaaggctga 240